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RESEARCH ARTICLE

Pharmacokinetics of a novel liquid controlled release codeine formulation

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Abstract

Codeine is an important opioid anti-tussive agent whose short half-life (2.9 ± 0.7 h) requires that it be administered at 4-h intervals when formulated as a simple aqueous solution. Liquid controlled release codeine formulations such as an older Codipertussin® formulation, which contained codeine bound to an ion exchange resin and coated with a retardant polymer, achieved an equivalent bioavailability when administered every 12 h. An accompanying paper described the development and *in vitro* characterization of a novel Codipertussin® formulation containing a non-coated codeine:ion exchange resin (Amberlite IR 69 F) complex. In this study, the bioavailability of codeine from this new liquid controlled release formulation was investigated in an open label, single center, randomized, steady-state, cross-over study in healthy male volunteers. Participants received either 69.7 mg codeine as the controlled release liquid form every 12 h or 23.2 mg codeine in solution every 4 h. Controlled release from the suspension of beads protracted the apparent mean half life of codeine from 3.2 h to 8.2 h, while the mean $AUC_{0-12\,h}$ was unchanged. *In vivo* codeine release profiles were further derived by the numerical deconvolution method, using the data from the drug solution as weighting function for the body system. Comparison of the data obtained with the *in vitro* release data presented in our earlier work showed an acceptable *in vitro–in vivo* correlation, which was described as *in vitro–in vivo* relationship, indicating the power of the *in vitro* method to predict *in vivo* pharmacokinetic behavior.

Keywords: Codeine, pharmacokinetics, oral suspension, sustained release

Introduction

The opiate drug codeine is one of the most important currently available cough-suppressing (anti-tussive) agents. Its relatively short plasma half-life (2.9 ± 0.7 h[1]) has prompted the development of sustained release formulations to increase compliance, in particular among children, older persons and disabled or incapacitated patients.

Successfully developed sustained release codeine preparations include so-called liquid controlled release codeine formulations[2] such as Codipertussin® cough syrup and concentrate drops. These preparations contain codeine bound to an ion exchange resin and coated with a retardant, Eudragit R100. The delayed codeine release and absorption obtained through this physical process is further extended by the diffusion barrier or bioerosion of the coating agent. Although these proven formulations effectively reduce the dosing frequency necessary to maintain plasma codeine levels, their commercial viability and thus their continued availability has, however, been threatened by modern manufacturing regulations, which require the strict containment of the solvents used for the coating procedure.

A solution to this problem would be provided by the identification of an alternative codeine-binding resin with ion exchange properties providing modified release kinetics of codeine without Eudragit coating. In an accompanying manuscript using an established *in vitro* drug release procedure (the USP XXIII paddle method[3]), we describe the identification of Amberlite IR 69 F as a

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resin able to produce modified release kinetics up to 8 h. These properties were observed both in a simple aqueous buffer and in syrup liquid drug formulations (230 and 697 mg codeine base/100 ml, respectively). The new formulations were moreover shown to be stable for at least 6 months.

The principal objective of the work described in this manuscript was to compare the pharmacokinetics of the new codeine cough syrup formulation with an aqueous solution of codeine in a clinical study in human volunteers with a view to confirming delayed release *in vivo*. Codeine pharmacokinetic data have been previously reported in a number of publications[1,4–12]. Band et al.[13] compared the pharmacokinetic parameters of codeine in humans following the administration of immediate release and sustained release dosage forms. Recently, the preparation of a codeine resinate sustained release suspension, and its pharmacokinetic evaluation in beagle dogs was described[14].

The second study objective was to examine the degree to which the *in vitro* results could be used to predict the results of the *in vivo* bioavailability study by the performance of a so-called *in vitro–in vivo* correlation (IVIVC). An IVIVC usually comprises a robust, direct relationship of a dissolution characteristic (*in vitro*) and an *in vivo* performance parameter, which can be used as a tool for quality assurance. A level a IVIVC relates the entire *in vitro* release profile with the corresponding plasma concentration profile. The link between these profiles is the *in vivo* release kinetics of the drug from the formulation. These can be calculated using the model independent numerical deconvolution technique based on the trapezoidal formula[15]. In this mathematical process, the mean plasma concentration profile from the oral solution of codeine phosphate (calculated as base) serves as the weighting function of the body system, i.e. the response to the fastest input. Since a modern IVIVC require a set of at least three different drug formulations, we described our results as an *in vitro–in vivo* relationship (IVIVR).

Materials and methods

Study design

An open label, single center, randomized cross-over study with repeated administrations separated by a 10-day washout period was approved by the Ethics Committee of the Medical Faculty of the University of Graz and conducted at the "Hansa" hospital in Graz in accordance with all applicable regulations (Declaration of Helsinki, 1964). The study was carried out on an ambulatory basis with the exception of the last 12 h, during which the subjects were confined to the hospital for blood sampling.

Each volunteer received a total of 418.2 mg of codeine over a 72-h period. The reformulated codeine cough concentrate described in the accompanying manuscript[3] (10 ml containing 69.7 mg codeine base) was administered at 12-h intervals, whereas the reference medication (10 ml solution of codeine phosphate containing 23.2 mg codeine) was given every 4 h. Each 12-h dose of the controlled release formulation was thus equivalent to three doses of the codeine phosphate solution. Both test and reference medications were taken with 200 ml of tap water under the supervision of the study nurse.

Blood samples were obtained via an indwelling catheter for the determination of plasma codeine levels (7 ml to enable repeat measurements). The first samples were taken from volunteers who received the delayed release formulation immediately before the administration of the 6th dose and from those who received the reference medication just prior to the 16th dose. Further samples were collected from both groups 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 8.5, 9, 9.5, 10, 11 and 12 h after these initial samples.

Subjects

Sixteen healthy males participated in the study after having signed informed consent. Their body weights ranged from 59–89 kg and were thus within ±10% of normal values as defined by the 1983 Metropolitan Insurance tables. Mean height was 180 cm (168–192 cm), and mean age was 25 years (21–34 years). All subjects were free from and had not previously suffered from clinically significant diseases according to the results of a physical examination, an electrocardiogram and laboratory tests and inspection of their medical histories and were either moderate or nonsmokers. The volunteers consumed only light meals prior to and during the study and took no other medication and refrained from alcohol throughout.

Analytical methods

Plasma codeine concentrations were determined by high-performance liquid chromatography (HPLC) and mass spectroscopy. Sample aliquots of 1.0 ml were adjusted to pH 10 by addition of 1.0 ml ammonium acetate buffer (0.5 M, pH 10) and extracted with 7 ml diethylether. After a short centrifugation step and freezing of the aqueous phase the organic phase was evaporated to dryness in a stream of nitrogen (35°C) and reconstituted with 0.25 ml of a mixture of acetonitrile and ammonium acetate (5 mM pH 2.1; 1:1 v/v). Fifty microliter of the reconstituted extract was injected onto a cyanopropyl column (Phenomenex Ultremex 5 CN, 250 × 4.6 mm). The mobile phase (0.9 ml/min, split approximately 1:4 after the column) consisted of two parts acetonitrile and eight parts ammonium acetate buffer (5 mM, adjusted to pH 2.9 with formic acid). Codeine (lead ion m +300) was monitored in electrospray/SIM mode. The calibration curve, which was linear over a range of 5.9–295 ng/ml with the quantification limit set at 5.9 ng/ml, was freshly prepared on each working day and used if the accuracy of the back calculated concentrations were within ±15% of the target values. Sample measurements were accepted as valid if the measurement values obtained for control (QC) samples (3 × 3 per 100 samples) were within ±20% of their respective nominal values.

Pharmacokinetic assessment and statistical methods

The pharmacokinetic parameters of codeine were determined from the plasma concentration data using the templates of the software Kinetica 3.0 for noncompartmental analysis. The maximum concentration C_{max} (ng/ml) and the time of the maximum concentration t_{max} (h) were reported as observed. The area under the plasma concentration versus time curve was calculated using the linear trapezoidal rule from time 0 to 12 h (16th to 18th or 6th dose interval, respectively). The apparent terminal elimination half-life $t_{½}$ (h) was calculated as $\ln 2/k_{el}$ and k_{el} was in turn obtained from the least squares regression analysis of the concentration-time data during the elimination phase. Values for C_{max}, t_{max} and $t_{½}$ for the reference medication (codeine solution) were calculated individually for the 16th, 17th and 18th dose interval and are given as their individual means in Table 1. The geometric mean ratio of the $AUC_{0-12\,h}$ for codeine was used to estimate the relative bioavailability for codeine solution and codeine controlled release. Descriptive statistical parameters (mean and standard deviation) were calculated using Statgraphics Plus 5.0.

In vitro release studies

The kinetics of *in vitro* codeine release from the drug:resin complexes were determined using the USP XXIII apparatus 2 method <724>. The apparatus used (Pharma Test Type PTWS III C) was operated at a release temperature of 37 +/– 0.5°C and a stirring speed of 100 rpm. Each of the six vessels was initially filled with 750 ml 0.1 N hydrochloric acid. After 2 h, the pH was raised from 1.2 to 6.8 by adding 250 ml of tris-phosphate-dodecahydrate buffer. Samples of 1.0 ml were taken at time 0 to determine the initial concentration and subsequently at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h, centrifuged for 10 min at 14,000 rpm and codeine determined by HPLC. The withdrawn sample volume was replaced by fresh medium.

IVIVR

The *in vivo* release kinetics from the resinate were calculated using the model independent numerical deconvolution technique based on the trapezoidal formula, as described in detail by Langenbucher[15]. For the development of the IVIVR, the percentages released *in vivo* were plotted against percentages released *in vitro* reported in our earlier work for the same time points. The quantitative relationship between the calculated *in vivo* release data and the measured *in vitro* release data was obtained by a linear least-square regression. All calculations were performed with Microsoft Excel, Kinetica version 4.0, InnaPhase Co. Philadelphia, PA, USA, and Statistical Analysis System, SAS release 8.2, SAS Institute Inc., Cary, NC, USA, enhanced with numerous macros written in SAS/IML program language by Dr. F. Langenbucher of BioVista LLC.

Table 1. Pharmacokinetic parameters (mean ± standard deviation, $n = 16$) of codeine following administration as a liquid controlled release form or as solution in steady state).

	Codeine solution	Codeine controlled release Codipertussin®
AUC 0–12 h (ng·h/ml)	694 ± 514	697 ± 372
C_{max} (ng/ml)[#]	79 ± 51	96 ± 57
T_{max} (h)[#]	1.2 ± 0.5	2.9 ± 0.64
t ½ (h)[#]	3.16 ± 1.43	8.2 ± 4.03

[#]Mean of all three 4-h profiles in 16th, 17th and 18th dose interval.

Results

Bioavailability of free and liquid delayed release codeine

The mean steady-state plasma concentration-time profiles of codeine obtained following administration of the new codeine cough syrup formulation (codeine loaded Amberlite IR 69 F beads) and an aqueous codeine solution are shown in Figure 1.

The derived mean pharmacokinetic parameters are listed in Table 1. Administration of 10 ml of the test formulation (corresponding to 69.7 mg codeine) produced a mean plasma codeine peak of 96 ng/ml after 2.9 h (±0.64 h) with a standard deviation of about 57 ng/ml. Twelve hours after the administration of the final dose of the test formulation the mean plasma concentration of codeine was still 33 ng/ml (±18 ng/ml).

As can be seen in Figure 1, the achievement of comparable plasma concentrations of codeine with the administration of a simple codeine solution required the administration of 23.2 mg of codeine every 4 h. The mean maximal concentrations in this case were 79 ng/ml (±51 ng/ml) appearing 1.2 h (±0.5 h) after each administration. The 95% confidence interval of the geometric mean ratios of the $AUC_{0-12\,h}$ was 0.76–1.28, which is within the extended limits of bioequivalence.

IVIVR

A comparison of the calculated *in vivo* codeine release profile from the resinate beads with the *in vitro* release profile described earlier by our group is shown in Figure 2. The *in vitro* release profile is the mean of 6 determinations. 10.85% of the codeine was present in an unbound form. This unbound fraction resulted in an initial onset of the plasma codeine within 30 min. Further, as shown for both *in vitro* and *in vivo* profiles, a pH dependent release was apparent. After 3 h *in vivo*, transit to the small intestine was observed as a decreased release rate. *In vitro*, the corresponding pH shift to pH 6.8 was established after 2 h according to USP XXIII rotating paddle method <724>.

In order to obtain an objective, quantitative measure of the degree of correlation of the *in vitro* and *in vivo* codeine release data, these were plotted as a linear least-square regression using the equation $y = 0.4797x + 17.22$ with a regression coefficient of $R^2 = 0.98$ (Figure 3). The 0/10.85% point was omitted from the regression analysis, so that

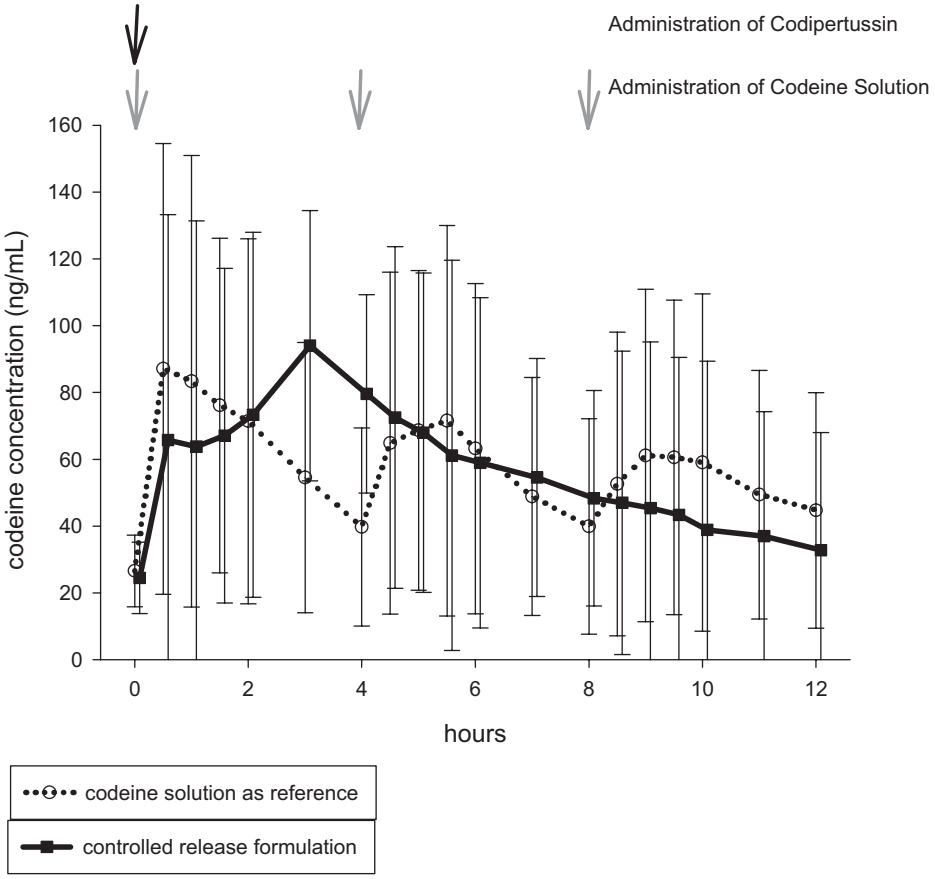

Figure 1. Mean plasma codeine concentrations on day 3 of repeated administrations of Codipertussin® or codeine solution every 12 h or every 4 h, respectively (mean ± standard deviation).

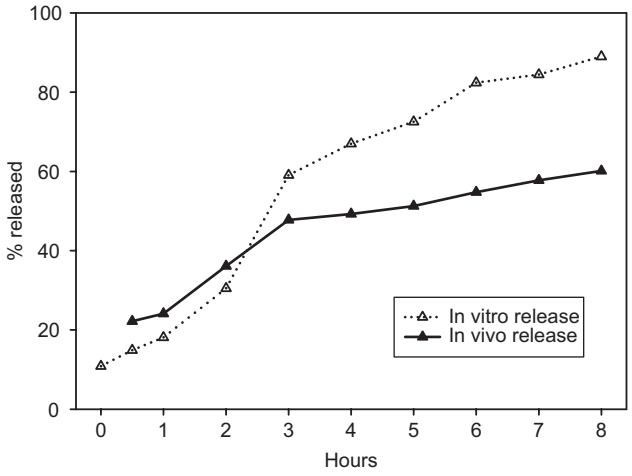

Figure 2. *In vitro* release data compared with the *in vivo* release profile calculated by deconvolution.

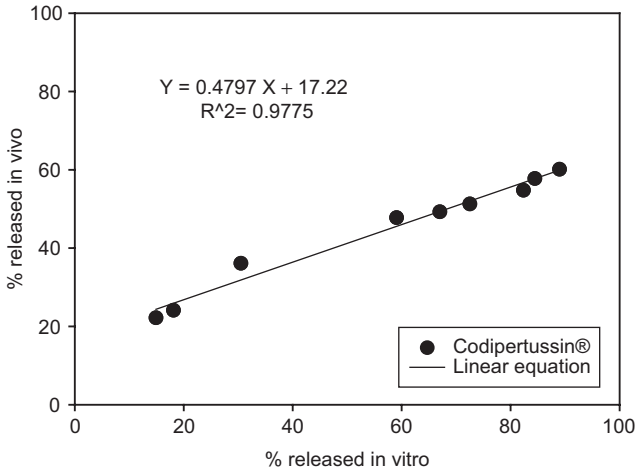

Figure 3. IVIVR model—correlation between percent dose released *in vivo* (Y-axis) and percent released *in vitro* (X-axis); regression equation: $y = 0.4797x + 17.22$; $R^2 = 0.98$.

the correlation represents only the modified release portion of the Codipertussin® product.

Discussion

Cough-suppressing agents are among the most widely used medications with annual sales in the USA alone in excess of $2 billion dollars[16]. Codeine, an opiate drug with both analgesic and cough suppressant activities, is one of the most important drug in this class. The widespread use of codeine has been facilitated by the development of effective delayed release formulations that overcome the potential for compliance problems among certain patient groups caused by the drugs short plasma half-life.

The goal of the work presented in this study and an accompanying manuscript[3] was to "modernise" an older liquid delayed release codeine formulation

(Codipertussin), i.e. to identify an alternative ion exchange resin for codeine loading that does not require subsequent polymer coating to achieve the desired delayed drug release profile. In our earlier study, the preparation and characterization of such a novel formulation was described comprising codeine bound to Amberlite IR 69 F beads and suspended in cough syrup at two different concentrations. On the basis of *in vitro* release studies, this new formulation provides a delayed codeine release profile equivalent to that of the original formulation. In the present paper, we firstly explored the bioavailability of codeine provided by this new formulation with reference to that obtained with the drug in aqueous solution.

The pharmacokinetic parameters for codeine solution reported here (C_{max} 79 ng/ml, t_{max} 1.2 h, $t_{½}$ 3.16 h following a dose of 23.2 mg) are in good agreement with published results[13].

Plasma levels of codeine in Figure 1 show an unexpected result as mean plasma levels and thus the AUCs seem to be consecutively lower. This finding is surprising as steady state can be assumed after five half-lives. A comparison of the AUCs using Student's *t*-test for paired comparisons did not show statistical significance, but unfortunately the power of the test is negligibly small due to very large variability in the data. The reason for this result may be due to influence of diet but remains unexplained. The large variability also affects the estimation of bioavailability. The 95% confidence interval of the $AUC_{0–12\,h}$ was found to be 0.76–1.28. A formal bioequivalence test was not planned in the protocol, so the result may be taken as a reasonable indication of bioequivalence between three doses of codeine every 4 h and one dose of Codipertussin® in the same time span. Problems with the method of determination can be excluded as LC with mass selective detection is state of the art in the analysis of opioids.

As well as considering the bioavailability of codeine, we calculated the *in vivo* release profile for codeine and compared this to the *in vitro* release profile described earlier[3]. Although the bioequivalence study had not been designed with the development of an IVIVC in mind, and although only one extended release formulation was tested in the absorption study, the *in vitro* and *in vivo* data sets could be mathematically correlated and were expressed as IVIVR. The objective was to determine the predictive power of the former: a high degree of correlation between *in vitro* and *in vivo* data would provide a rationale for future formulation work to rely on *in vitro* release data and the avoidance of time-consuming human studies. The *in vivo* release data were derived by the numerical deconvolution method using the data from the drug solution as weighting function for the body system. Comparison of the *in vitro* and *in vivo* data showed an IVIVR, demonstrating that the *in vitro* release measurements faithfully predicted the performance of the new codeine delayed release formulation *in vivo*. The *in vitro* method can thus be considered biorelevant. Furthermore, the release of codeine from the resinate formulation is indeed the rate controlling step for the subsequent absorption process.

In summary, in this study the bioavailability and retard profile of codeine from this new liquid controlled release formulation was demonstrated. The mean half-life of codeine was increased from 3.2 h to 8.2 h. Additionally, acceptable IVIVR data for our delayed release resinate were determined. This will offer a cost reduction in production/quality control as well as further development of new codeine formulations due to the predictive value of our correlation method.

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Declaration of interest

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