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Influence of cholestyramine on the pharmacokinetic parameters of cefadroxil after simultaneous administration

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Summary

Cefadroxil is a semi-synthetic cephalosporin destined for oral administration. When 500 mg of the drug are administered by this route in volunteers, with normal renal function, the following average pharmacokinetic parameters are obtained: $K_a = 1.265\ h^{-1}$; $C_{max} = 10.073\ \mu g/ml$; $t_{max} = 1.139$ h; $K_e = 0.592\ h^{-1}$ and lag time = 0.252 h. Joint administration of this drug with cholestyramine causes interference in the absorption process which is principally manifested in a statistically significant increase in the lag time, though the bioavailability of the drug remains unaltered.

Introduction

Destined for oral use, cefadroxil is a semi-synthetic cephalosporin whose structure is 7-[D-(−)-α-amine-α(4-hydroxyphenyl)-acetamido]-3-methyl-3-cephem-4-carboxylic acid. Its antimicrobial spectrum includes both Gram-negative and Gram-positive microorganisms generally associated with infections of the respiratory and urinogenital tracts.

After oral administration, it is absorbed rapidly and totally (Mariño et al., 1980). The serum half-life has an average value of 1.13 ± 0.21 h, greater than that obtained for other oral cephalosporins such as cephalexin, cephradine (Pfefer et al., 1978), cefaclor (Hodges et al., 1977) and cefroxadine (Wirtz, 1977). The serum protein binding capacity of cefadroxil is low and it does not undergo any metabolic process within the organism, being excreted in a unaltered state principally through the kidneys (Pfefer et al., 1978).

Cholestyramine is a synthetic, strongly basic anion-exchanging resin containing quaternary ammonium functional groups which are attached to a styrenedivinylbenzene copolymer. Its use in clinical practice is recommended due to its capacity to retain intraluminal biliary acids, thereby forming a complex which is neither digested nor absorbed, for the reduction of blood cholesterol levels and in the treatment of pruritis caused by biliary stasis.

Because of its adsorbent properties, it is unadvisable to administer this product jointly with other drugs in order to avoid possible interactions, as reported by Zurier et al. (1965) when administered simultaneously with soluble vitamins or, as is the case of the interference with the absorbance of iron (Thomas et al., 1972) and, more specifically, the modification of certain antibiotics, such as cephalexin (Parson et al., 1975).

The aim of the present work was to study the possible modifications in the pharmacokinetics of cefadroxil after simultaneous administration with the resin cholestyramine.

Materials and Methods

In vitro studies

The in vitro adsorption of cefadroxil by cholestyramine was assayed by treating 100 mg of the resin with a 4×10^{-3} M solution of the antibiotic. The pH of the solution was adjusted to the following values: 3.0, 6.0 and 8.0. The suspension obtained was shaken for 1 h at 40°C in a water bath, after which the free cefadroxil in the supernatant fluid was determined. At the same time, the I.R. spectrum of cefadroxil followed by that of cholestyramine were obtained, together with those of the complexes formed by them at the different pH values established with an I.R. spectroscope (mod. double-beam Beckman Acculab 6 using KBr discs).

The I.R. spectrum of cefadroxil has the following characteristic bands: strength vibration of the –OH group at 3500 cm^{-1}; strength vibration of the –NH group at 3200 cm^{-1}; beta-lactam ring at 1750 cm^{-1}; strength vibration of the –CO group at 1600 cm^{-1}; strength vibration of the C–N bond and flexion of the NH group at 1550 cm^{-1}.

In vivo studies

The in vivo studies on the interaction between cefadroxil and cholestyramine were carried out with a cross-over design experiment involving 4 volunteers with normal renal function; creatinine clearance was greater than 90 ml/min. Age ranged between 20 and 23 years and average weight was 67 kg. In all cases involved consent was obtained from the participants prior to inclusion in the study.

The cross-over design involved each individual undergoing a total of 2 experiments in which 500 mg of cefadroxil and 10 g of cholestyramine plus 500 mg of the antibiotic were administered. The latter was administered orally in capsule form accompanied by 250 ml of water. All subjects fasted for 12 h before the study.

There was an interval of 12–15 days between each experiment. It was ascertained

that none of the volunteers had received any medication for at least 72 h prior to the experiment.

Blood samples were collected at the following times: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0 and 7.0 h after administration and urine samples were collected during the periods 0–1, 1–2, 2–4, 4–6, 6–8, 8–10, 10–16, and 16–24 h after administration of the antibiotic. All volumes of urine were stored at −20°C before analysis.

Microbiological assay

Determination of the antibiotic was carried out with a microbiologic plate diffusion method using *Bacillus subtilis* (ATCC no. 6633) as the test organism. Standard curves of the antibiotic in solutions equal to those of the problem samples were made up with known concentrations of the antibiotic. All determinations were performed a minimum of 4 times.

Repeated analyses of the reference standards indicate that the precision expressed as relative standard deviation was 5%. The lowest sensitivity limit of the method was 1.60 μg/ml.

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated using a programmable Hewlett-Packard 97 calculator (Foster et al., 1977).

Results and Discussion

The serum levels of cefadroxil as a function of time after oral administration in capsule form follows a single-compartment open kinetic model, according to the criteria of Akayke (Yamaoka et al., 1978) independently of whether the antibiotic is administrated simultaneously with cholestyramine or not.

Fig. 1 shows the serum levels curves of cefadroxil in each of the volunteers in the

TABLE 1

PHARMACOKINETIC PARAMETERS OF CEFADROXIL IN THE 2 GROUPS OF VOLUNTEERS STUDIED, OBTAINED FROM THE SERUM CONCENTRATIONS OF THE ANTIBIOTIC

	With cholestyramine				Without cholestyramine		
	J.R.S.	J.S.H.	C.C.M.	J.D.P.	$\bar{X}$		S.D.
K_a (h^{-1})	2.077	1.511	1.363	2.212	1.265	±	0.090
C_{max} (μg/ml)	11.210	8.569	13.824	15.830	10.072	±	2.274
t_{max} (h)	0.957	1.119	1.191	0.887	1.139	±	0.090
t_0 (h)	0.705	0.908	1.432	1.436	0.252	±	0.021
K_e (h^{-1})	0.429	0.473	0.471	0.473	0.592	±	0.121
$(AUC)_0^\infty$ (μg/ml)h	40.430	33.750	54.181	50.840	40.602	±	10.296

K_a, absorption constant; C_{max}, maximum serum concentration reached at t_{max}; t_0, lag-time; $(AUC)_0^\infty$, area under the curve of the serum level–time.

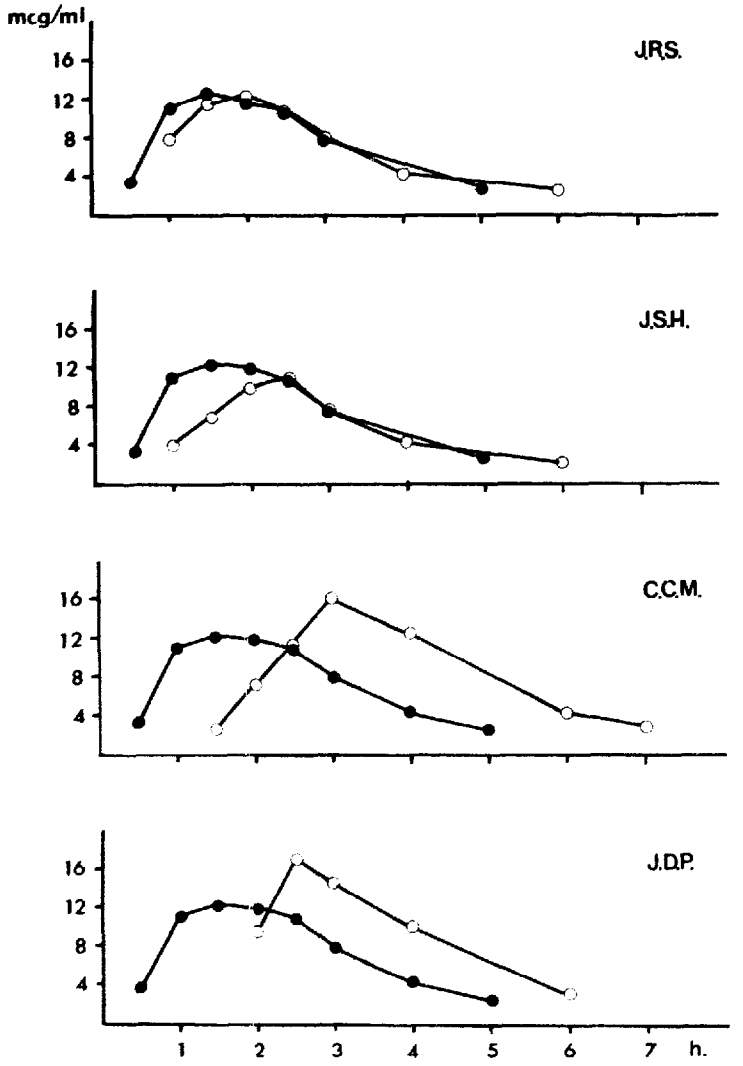

Fig. 1. Serum level curves of cefadroxil after simultaneous administration with the resin (○) compared with the average serum levels curve obtained after administration of the antibiotic alone (●).

study after joint administration with cholestyramine compared with the average serum levels curve of the antibiotic obtained in the absence of resin.

Similarly, Table 1 shows the pharmacokinetic parameters obtained from the values of the serum concentrations reached by the antibiotic in each of the volunteers administered jointly with the antibiotic and the resin compared with the average pharmacokinetic parameters obtained in the same way in individuals to whom only the antibiotic was administered.

After the *t*-test statistical study of the various pharmacokinetic parameters, it was seen that the only statistically significant difference ($P < 0.05$) is that found for the values of the lag-time (t_0) between the two groups studied. When cholestyramine is administered simultaneously with the antibiotic, the time elapsing before the latter

appears in blood is considerably greater than when the antibiotic is administered alone. Such a variation in the lag-time, independent of some mechanical effect, may be attributable to a reversible equilibrium:

cefadroxil + cholestyramine ⇄ complex

This equilibrium will be governed by the pH values prevailing at the site of adsorption. Furthermore, due to the zwitterionic nature of cefadroxil (Mariño et al., 1981), the relative ratio of ionized to unionized species will also be governed by the pH.

Accordingly, pH modifies two process: (1) the absorption of free cefadroxil not forming a complex; and (2) the formation of the cefadroxil–cholestyramine complex.

In turn, the latter process becomes, indirectly, another factor governing the absorption of the antibiotic.

In order to confirm the effect of pH on the formation of the complex, in vitro studies on the desorption of the complex were carried out a different pH values, as shown in Table 2; this also shows the binding percentages of the antibiotic to the resin obtained in this study. It may be seen that as the pH values rise, there is a considerable increase in the amount of antibiotic adsorbed. This is confirmed by the I.R. spectra of the different complexes, as shown in Fig. 2; it may be seen that the characteristic band of the beta-lactam ring is considerably reduced as the amount of antibiotic complexed with the resin decreases.

As the pH values rise, so does the adsorption of the antibiotic by the resin, while at acid values, the complex is formed to a much lesser extent.

In the zone of the G.I. tract where absorption may take place, the antibiotic is principally found in the free state. The fraction to be found complexed with the resin will undergo progressive release (desorption), thus permitting its absorption by the organism. Towards the end of the G.I. tract, where high pH values are reached, would be the most favourable site for the formation of the complex, though by this time, the absorption process of the antibiotic should be practically complete.

As a consequence of this, though there is a delay in absorption when the two products are administered concurrently, at the end of the process the amount adsorbed is similar in both groups, as shown by the values obtained for the area under the curve of serum levels versus time which do not show any statistically significant differences ($P < 0.05$).

TABLE 2

PERCENTAGE OF CEFADROXIL ADSORBED BY THE RESIN AS A FUNCTION OF THE pH VALUES STUDIED

pH	% adsorbed
8.0	54.4
6.0	16.5
3.0	4.0

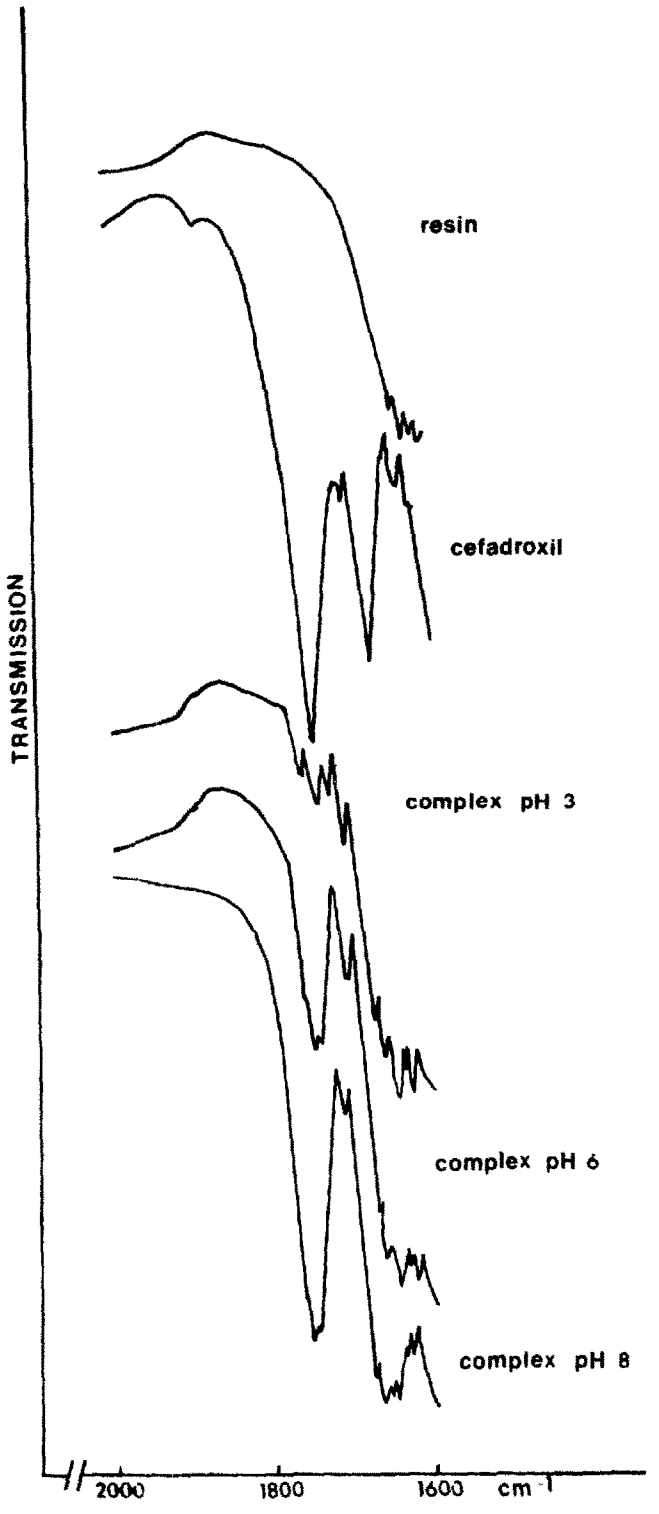

Fig. 2. Variation in the I.R. spectrum of the antibiotic-resin complex as a function of the pH studied.

TABLE 3

PHARMACOKINETIC PARAMETERS OF CEFADROXIL IN THE 2 GROUPS OF VOLUNTEERS STUDIED, OBTAINED FROM THE URINARY LEVELS OF THE ANTIBIOTIC

	With cholestyramine				Without cholestyramine		
	J.R.S.	J.S.H.	C.C.M.	J.D.P.	$\bar{X}$		S.D.
K_u (h^{-1})	0.355	0.368	0.385	0.387	0.400	±	0.015
V_{max} (mg/h)	134.710	114.718	114.754	92.425	116.950	±	17.276
t_{max} (h)	1.224	2.136	2.043	2.360	< 1.000		
% excreted at 24 h	98.030	76.600	77.000	64.000	83.813	±	10.245

K_u, urinary excretion rate constant; V_{max}, maximum urinary excretion rate reached at t_{max}.

Once the antibiotic has reached the systemic circulation, its behaviour becomes independent of whether it has been jointly administered with the resin or not, as is shown by the values obtained for the various pharmacokinetic parameters which have no statistically significant differences between both groups.

Our results agree with those reported by Parson et al. (1975) for the joint administration of cephalexin and cholestyramine. In their study, an increase in the lag-time and a decrease in absorption were also observed; similarly, the area under the curve of the serum levels versus time curve is not modified by the presence of the resin and neither is the amount of drug excreted in urine altered.

Table 3 shows the pharmacokinetic parameters obtained from the antibiotic levels in urine for each of the volunteers jointly administered with cefadroxil and resin compared with the average pharmacokinetic parameters obtained analogously in those individuals receiving antibiotic alone.

The evolution of the drug levels in urine, in those cases where the drug is not modified and in which the drug is principally excreted by the kidney are a true reflection of the drug's behaviour in the systemic circulation. Thus in this case, a delay may be seen in the time at which the maximum urinary excretion is reached (V_{max}), precisely as a consequence of the increase in lag-time. Furthermore, the urinary excretion constant shows no statistically significant differences between the two groups studied and is very similar to the value obtained for the elimination of the drug from serum. Because of this, the percentages of drug excreted in urine do not show any statistically significant differences between the two groups, similar to the afore-mentioned case of cephalexin.

From the above, it may be concluded that these antibiotics should be added to the list of drugs that ought not to be simultaneously administered with cholestyramine; the degree of malabsorption that this compound produces fortunately does not appear to be of serious therapeutic import.

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