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CHOICE OF OPTIMUM PHARMACOKINETIC MODEL OF ORALLY ADMINISTERED PARACETAMOL

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ABSTRACT

The present work studies the characterization of the pharmacokinetic profile of paracetamol following oral administration of DUOROL® tablets containing 500 mg of the active compound. Analysis is made of the influence of statistical weighting on the selection of the pharmacokinetic model chosen. In the model proposed, the uptake of the drug into the systemic circulation is described by two first-order sequential kinetic processes. The values of the first order rate constants that define the absorption process have values of 4·79 and 9·73 h^{-1}. Validation of the absorption model proposed was performed by applying the Wagner-Nelson method, according to which values of 4·63 and 10·95 h^{-1} were obtained for each of the constants defining the uptake of the drug into the systemic circulation.

KEY WORDS Paracetamol Absorption Statistical weighting NONLIN AUTOAN

INTRODUCTION

Paracetamol is an antipyretic analgesic belonging to the group of derivatives of p-aminophenol. The drug is widely used in clinical practice and is considered to be a substitute for aspirin in patients with allergy, gastric alterations, and different disorders in their coagulation processes.[1]

Since its introduction in therapeutics numerous pharmacokinetic studies have been conducted in humans following administration of the drug through different routes and in different dosage forms.

Detailed analysis of such studies reveals that the evolution of the plasma levels of paracetamol after i.v. administration follows an open two-compartment kinetic model.[2] The fitting of the plasma levels values of the analgesic following intramuscular administration seems to be optimal when a two-compartment

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model is applied,[3] as is case for i.v. administration, but problems arise upon attempting to fit plasma paracetamol levels when the drug is administered orally in different dosage forms. Whereas in some studies optimal fitting is achieved with a single-compartment model,[4] in others the evolution of the plasma levels of the drug is better characterized by an open two-compartment model.[5]

These differences point to the complexity of the absorption processes of the drug and the higher number of factors that may condition the incorporation of this active ingredient into the systemic circulation and may even mask the drug's distribution characteristics and falsify the calculation of the parameters defining the absorption process.

Furthermore, Clements and Prescot[6] have demonstrated that pharmacokinetic analysis of the plasma levels obtained after i.v. administration of the drug depends on the statistical weighting function of each of the experimental points.

The principal aim of the present work was to select a suitable model which would allow us to make optimal fittings, on the basis of pharmacokinetic and statistical criteria, of the evolution of the plasma levels of the drug following administration to healthy volunteers in a new pharmaceutical form recently introduced onto the Spanish market.

MATERIAL AND METHODS

The study was performed following the administration of DUOROL® (Antibióticos S.A. Spain) containing 500 mg of paracetamol to five healthy volunteers. The volunteers had previously fasted overnight and gave informed consent to participate in the survey. Before participating in the study all were subjected to a battery of criteria regarding their inclusion or exclusion. Those included underwent an exhaustive clinical and laboratory checkup.

The analgesic was administered with 100 ml of water. Blood samples were collected at previously programmed times in heparinized tubes. Plasma was obtained by centrifugation and stored at -20° until analyzed.

Quantification of the plasma levels of paracetamol was performed by a gas chromatography technique using phenacetin (Merck) as internal standard. Extraction was performed with ethyl ether in basic medium and the paracetamol was later derivatized at 40° with acetic anhydride in pyridine.

The apparatus employed was a Varian Mod 3300 equipped with a specific phosphorus-nitrogen detector (TSD). The carrier gas was nitrogen at a flow rate of 40 ml min^{-1}. Working temperatures were as follows: 300° (injector), 275° (detector), and 195° (column). The glass column used had a length of 1·5 m and 3 mm interior diameter and was packed with 3 per cent OV–17 on Gas-Chrom Q 100/120 mesh.

Fitting of the experimental results to the pharmacokinetic models proposed was done using the NONLIN[7] and AUTOAN–NONLIN[8] programs based on the Gauss-Newton algorithm with the modification proposed by Hartley.[9]

Calculation of the fraction of drug absorbed per unit of volume was performed by the Wagner–Nelson method.[10]

RESULTS AND DISCUSSION

Figure 1 shows the evolution of the mean plasma levels of paracetamol obtained in the five volunteers. It may be seen that these levels apparently fit a single-compartment model. Fitting was therefore carried out according to this pharmacokinetic model using three different weighting factors: 1, $1/C$, and $1/C^2$, the latter being the most suitable factor of the three as seen by replicate analyses of plasma samples containing known concentrations of paracetamol.

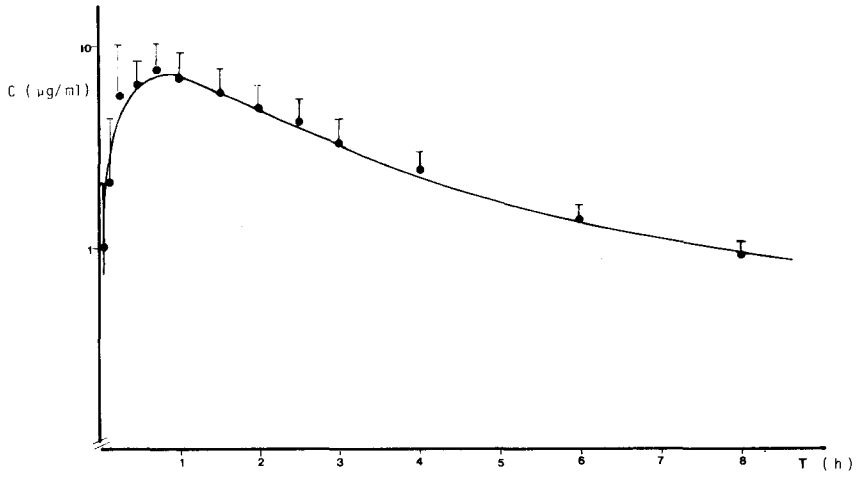

Figure 1. Evolution of the mean plasma levels of paracetamol following administration of a dose of 500 mg in DUOROL® tablets

Figure 2 shows the results obtained after fitting; it may be seen that when the first weighting factor is used the first stretch of the curve is better fitted but that there is a deviation in the part corresponding to elimination, yielding a half-life value of 1·7 h. By contrast, as the weighting factor is modified better fitting occurs in the final part of the curve, obtaining half-life values of 2·2 and 2·9 h —more in accordance with those reported by other authors[11] — while there is a clear discrepancy between the theoretical and experimental values corresponding to the absorption phase.

The fact that fitting is not optimal when the most appropriate weighting factor is used shows that the model employed is not the correct one and points to the

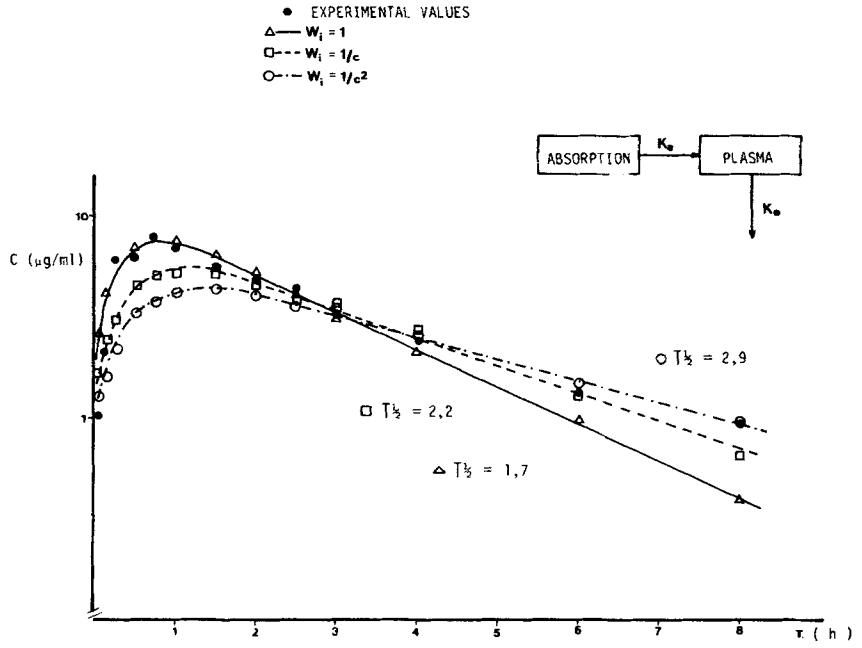

Figure 2. Theoretical curves obtained by fitting of experimental data to a single-compartment open kinetic model with first-order absorption and using three different weighting factors

errors that can be made in the interpretation of the evolution of drug plasma levels if, firstly, suitable statistical criteria are not taken into account and, secondly, if a series of systematic operations is not performed in the pharmacokinetic analysis; these may be summarized as follows:

1. Demonstration of the presence or absence of Michaelis-Menten kinetics.
2. If elimination follows first-order kinetic processes, one must determine the optimum number of terms in the polyexponential equation and calculate the numerical values of the exponentials and coefficients.
3. Selection of the appropriate pharmacokinetic model and obtention of the initial estimates of the parameters.
4. Fitting of the experimental data to the equations describing the pharmacokinetic model proposed by use of non-linear regression programs and later analyzing the results obtained.

It is undoubtable that carrying out this set of operations is a laborious and complex procedure. However, currently there are computer programs that are able to perform the above-mentioned operations automatically and select, rapidly and with great precision, the most suitable pharmacokinetic model.

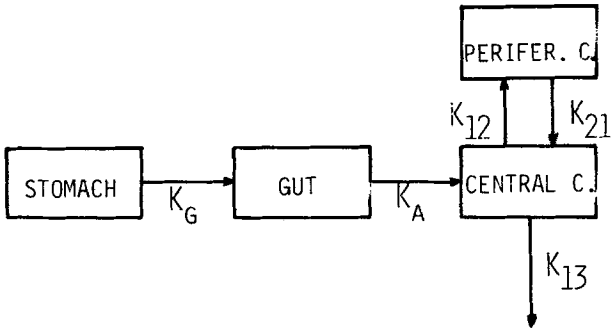

Figure 3. Pharmacokinetic model selected with the AUTOAN program to describe the evolution of the plasma levels of paracetamol

Accordingly, in the second step of the study we analysed our experimental results with the AUTOAN program using the three weighting factors used in the first fitting so that the program would select the most appropriate pharmacokinetic model. In all cases the AUTOAN program selected the model shown in Figure 3, similar to that described by Clements *et al* (12); this shows two sequential kinetic processes during the absorption phase defined and characterized by their corresponding first-order rate constants (K_1 and K_2). Figure 4

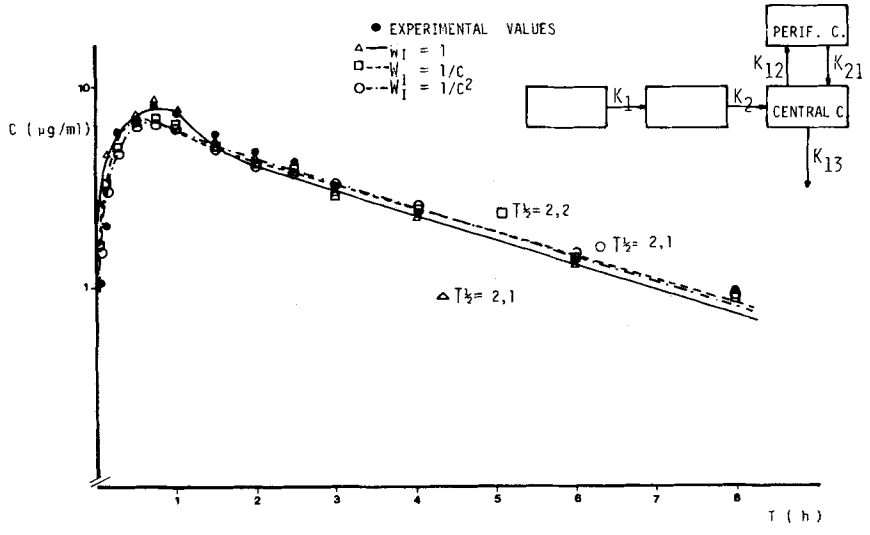

Figure 4. Theoretical fitting and experimental values obtained using a two-compartment open kinetic model with two sequential kinetic processes of absorption for the three weighting factors employed

shows the excellent correlation between the experimental and theoretical values both in the elimination phase, with half-life values of 2·1, 2·2, and 2·1 h (similar to those reported in the literature[11]), and on the ascending stretch of the curve, with values for the three rate constants as shown in Table 1 for the three weights employed.

Table 1. Values of the absorption constants for the pharmacokinetic model chosen, calculated using three different weighting factors (1, 1/C and $1/C^2$)

$W_1 = 1$		$W_1 = 1/C$		$W_1 = 1/C^2$	
K_1 (h^{-1})	K_2 (h^{-1})	K_1 (h^{-1})	K_2 (h^{-1})	K_1 (h^{-1})	K_2 (h^{-2})
2·19	13·89	3·08	14·29	2·41	11·08
2·71	6·32	7·28	7·75	2·70	9·59
15·86	9·16	13·67	20·79	10·71	17·48
0·50	7·71	0·50	6·76	0·41	4·17
5·43	12·91	11·80	10·60	4·26	8·63
5·33	9·98	7·26	12·03	4·09	9·73

Table 2. Values of the rate constants defining the process of uptake of the drug into the systemic circulation (K_1 and K_2) calculated with the AUTOAN program and according to the Wagner–Nelson method.

	Wagner–Nelson		AUTOAN	
Volunteer	$K_1(h^{-1})$	$K_2(h^{-1})$	$K_1(h^{-1})$	$K_2(h^{-1})$
1	3·04	9·78	2·41	11·08
2	2·19	14·08	6·20	9·59
3	7·43	13·53	10·71	17·48
4	4·99	8·50	0·41	7·91
5	5·51	8·86	4·26	8·63
X	4·63	10·95	4·79	9·73
δ_n	1·85	2·37	3·52	1·37
δ_n-1	2·07	2·65	3·94	1·53

According to the interpretation of Clements *et al.*[12], the value of K_2 could represent the value of the true absorption constant while K_1 would be the rate constant of the limiting process.

Figure 5 shows the difference in fittings obtained with the weighting factor of the squared reciprocal of the concentration when the one-compartment model is employed together with a two-compartment model with two sequential absorption processes, the latter being the one that allows the best fit of the experimental results.

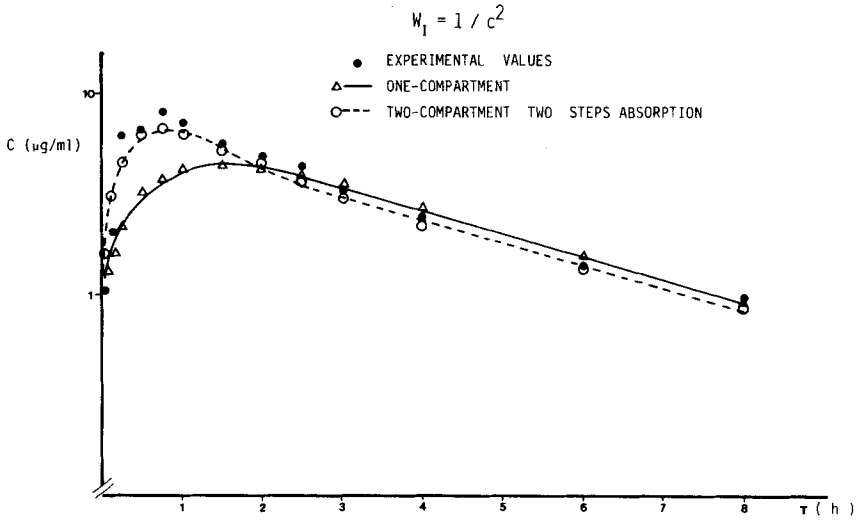

Figure 5. Difference between the fittings obtained using the optimum weighting factor for the two pharmacokinetic models studied

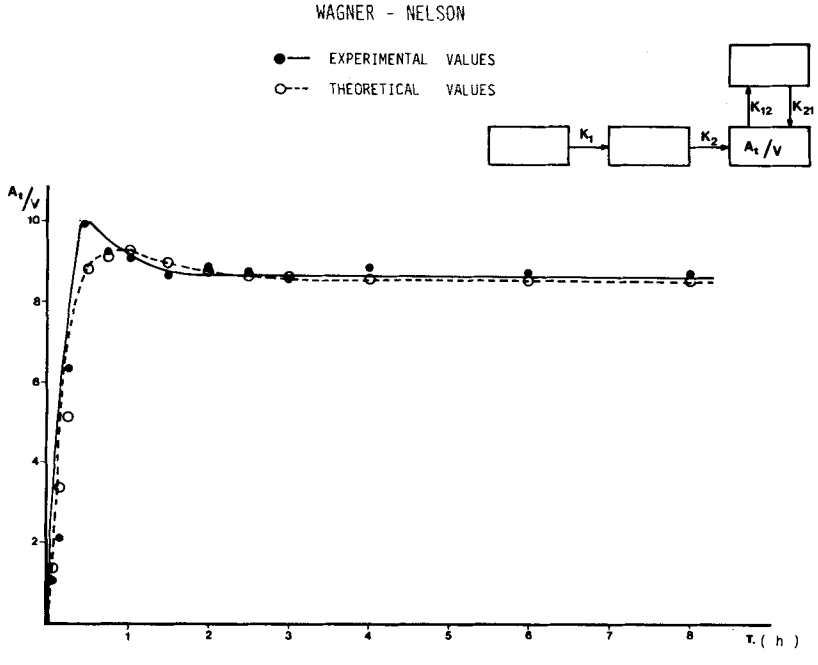

Figure 6. Evolution of the experimental and theoretical values after application of the Wagner–Nelson method and application of the absorption model proposed that considers two sequential kinetic processes.

In order to validate the pharmacokinetic model proposed, we applied the Wagner–Nelson method [10] to the plasma concentration-time data to obtain the amounts of drug absorbed per unit of volume as a function of time. Figure 6 shows the experimental values and the theoretical values calculated after applying an absorption model characterized by the presence of two sequential kinetic processes. As may be seen, there is good correlation between the rate constants obtained with this procedure and those obtained with the AUTOAN program, as shown in Table 2.

These findings allow us to accept the pharmacokinetic model proposed as valid to justify and reproduce the kinetic behaviour of paracetamol when administered in the dosage form studied in this work.

REFERENCES

1. J. Koch-Weser, *Med. Intelig.*, **295**, 1297 (1976).
2. M. D. Rawlins, D. B. Henderson, A. R. Hijab, *Eur. J. Clin. Pharmacol.*, **11**, 292 (1977).
3. R. A. Seymour, M. D. Rawlins, *Eur. J. Clin. Pharmacol.*, **20**, 215 (1981).
4. L. F. Prescot, *B. J. Clin. Pharmacol.*, **10** (suppl. 2), 2915 (1980).
5. B. Ammer, M. Divoll, D. R. Abernethy, D. J. Greemblat, L. Shargel, *J. Pharm. Sci.*, **72**, 955 (1983).
6. J. A. Clements, L. F. Prescott, *J. Pharm. Pharmac.*, **28**, 707 (1976).
7. C. M. Metzler, G. L. Elfrin, A. J. McEven, *Biometrics*, **30**, 512 (1974).
8. AUTOAN, *A Time-Sharing Digital Computer Program*, available from Publication Distribution Service, 615 East University Avenue, Ann Arbor, Michigan, 48106.
9. H. O. Hartley, *Technometrics*, **3**, 269 (1961).
10. J. G. Wagner, *J. Pharmacokin. Biopharm.*, **2**, 469 (1970).
11. A. J. Cummings, M. L. King, B. J. Martin, *B. J. Clin. Pharmacol.*, **29**, 150 (1967).
12. D. Clements, R. C. Heading, W. S. Nimmo, M. D. Prescott, *Clin. Pharmacol. Ther.*, **24**, 420 (1981).