DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(15-17), 2225-2239 (1988)

FORMULATION OF SUPPOSITORIES CONTAINING IMIPRAMINE AND CLOMIPRAMINE CHLORHYDRATES.

Chaumeil J.C., Khoury J.M., Zuber M., Courteille F., Piraube C., Gard C.
Département de Pharmacotechnie, Faculté des Sciences Pharmaceutiques et Biologiques, 4 av. de l'Observatoire 75006 Paris. - Pharmacie Centrale, 7 rue du Fer à Moulin 75006 PARIS.
Bellenger P.
Pharmacie, Hôpital St Louis, 2 place du Dr A. Fournier 75010 PARIS.

ABSTRACT

Imipramine chlorhydrate and clomipramine chlorhydrate could be formulated into suppositories forms. Their ability to be administered by the rectal way was assessed by the measurement of their hydrophilic/lipophilic partition coefficient and their diffusion coefficient with the Stricker's apparatus.The suppositories were formulated with several halfglycerides excipients. The selection of the formulae was carried out by using the following physicochemical tests : rheological behaviour, melting point, liquefaction time with the Krowczynski's technique, disintegration time with the Munzel's method, spreading area, hardness, kinetic of release. The bioavailability of the suppositories evaluated on rabbits

compared to an intravenous injection was 28% for Clomipramine and 25 % for Imipramine.
A clinical assay was carried out with three inpatients. The plasmatic levels of the drugs and the clinical efficiency were in the same range as previous data reported in the literature for oral forms.

INTRODUCTION

Imipramine and clomipramine are tricyclic antidepressants which are absorbed by passive diffusion almost completely by the small intestine. Because their slow elimination, mainly renal, their half-life is 6 to 15 hours for imipramine, and 17 to 28 hours for clomipramine (1).
These two parameters are in favor of the use of the rectal way for the administration of suppositories with these drugs.
The suppository form is really needed for depressive patients with an unaccessible digestive tract following a surgical operation or a functionnal insufficiency. For these patients, an oral form cannot be used. A parenteral form is difficult to use during a long time, according to the bad tolerance of those drugs in intravenous perfusion or intramuscular injection.
This study was developped into three steps :
- firstly, an in vitro study of the type of absorption of each drug was carried out ;
- secondly, the galenic formulation assays were done,
- thirdly, the bioavailability was determined on rabbits and clinical assessment were carried out.

MATERIALS

Clomipramine chlorhydrate and imipramine chlorhydrate were obtained from Ciba-Geigy France. The particule

size for both drugs was between 40 and 100 µm. Seven half synthetic glycerides were used : witepsols H5 (hydroxyl index, HI = 5), H15 (HI = 15), W25 (HI = 30) (Dynamit Nobel), and Suppocires AIM (HI = 6), NAI 10 (HI = 15), A (HI = 20-30), AP (HI = 30-50) (Gattefossé)

IN VITRO STUDY OF ABSORPTION

Measure of partition coefficient

Clomipramine and imipramine are basis. Their pKa is about 9.5. It was interesting to measure their partition coefficient between an aqueous solution of chlorhydrates and a lipophilic phase.

The measurements were carried out with a double compartiment device, using 25 ml horizontal pyrex tubes, placed in a circular stirrer (2).

The chozen aqueous phase was purified water, according to the unbuffered rectal liquid composition. The lipidic phase was the same as the Stricker's one : dodecanol 1p caprylic acid 4p (3). The following values were found for the partition coefficient of clomipramine : 132 ± 16 and 100 ± 5 for imipramine (averages of five measurements) in favour of the lipid phase. These molecules could be then absorbed rapidly through the mucosis membranes of the rectal tract.

Evaluation of the diffusion coefficient

The diffusion of clomipramine and imipramine, through the mucosis membranes was simulated with the Stricker's apparatus (Sartorius - France, Paris)(3). This device is constituted of two reservoirs, containing in the first one a 100 mg/100 ml solution of either drug chlorhydrate in purified water simulating the rectal liquid, and in the other one 100 ml of a simulated plasmatic liquid (which was a pH 7.4 buffer composed of 20.5 g of Na_2HPO_4,

$2H_2O$ and 2.8 g of KH_2PO_4 in 100 ml of purified water). Each solution was continuously stirred and circulated by the way of a peristaltic pump, on each side of a 40 cm² porous cellulosic membrane, impregnated with the lipid phase, simulating the rectal mucosa.

Five diffusion assays were carried out at 37° ± 0.5°C for each drug. The concentrations of the drug was measured in each medium, by UV spectrophotometry at 252 nm (Perkin Elmer 550, OSI, Paris), during 140 min.

The curves of the diffusion kinetic (Figure 1) exhibited three states :

- first, the impregnation state of the membrane by the drug,
- secondly, the state of the passive diffusion, with a first order kinetic,
- thirdly, the beginning of an equilibrium state.

The partition coefficients, Kd, were calculated between 20 and 50 min during the second state, in which the increase of the concentration in the plasmatic liquid is a linear function of the time.

Kd was calculated from the following formula :

$$\underset{(cm.min^{-1})}{Kd} = \frac{C_{P2}-C_{P1}}{T_2 - T_1} \times \frac{1}{C_{Ro}} \times \frac{V_{Ro}}{F}$$

C_{P2} and C_{P1} were the concentrations of the drug in the simulated plasmatic liquid at the times T_2 (50 min) and T_1 (20 min). C_{Ro} was the concentration of the drug in the simulated rectal liquid at the beginning of the assay (100 mg/100 ml). V_{Ro} was the volume of the simulated rectal liquid at the beginning of the assay (100 ml). F was the active area of the membrane (40 cm²).

The data showed that the Kd value of imipramine was $4.08.10^{-3}$ cm.min^{-1}. It is a mean value, according to

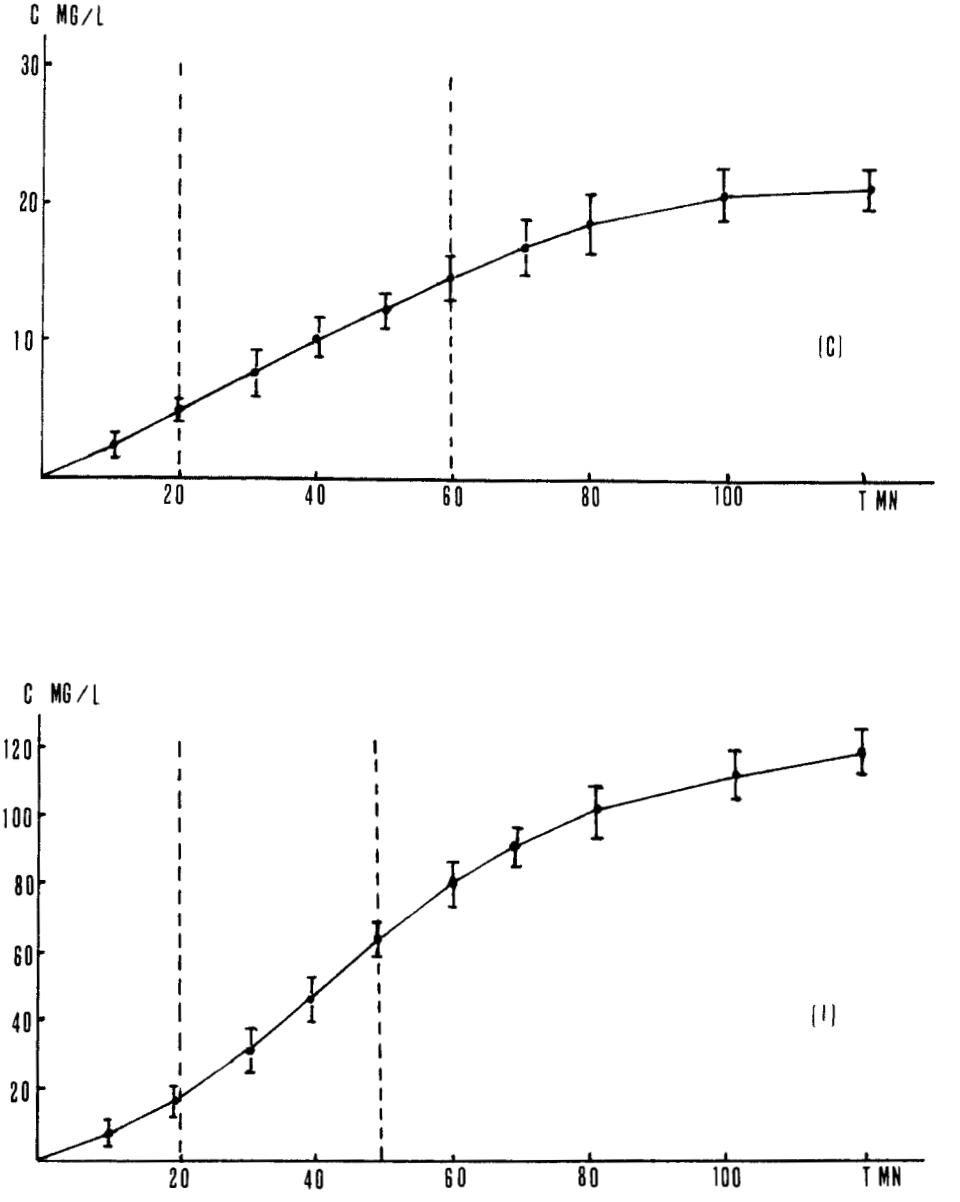

Figure 1 : Measurements of the kinetics of diffusion of clomipramine (C) and imipramine (I) in the "plasmatic" reservoir with the Stricker's apparatus.

Stricker's works(3). The Kd value of clomipramine was $0.7.10^{3}$ $cm.min^{-1}$: it is a weak value, according to Stricker's works.

Therefore imipramine exhibited a higher diffusion capacity than clomipramine.

Nevertheless, the measurements of the decreasing concentrations of the drugs in the simulated rectal phase, showed that there would be a leakage of the drugs in the impregnation lipophilic substances of the membrane, especially for clomipramine.

These results are in good correlation with those obtained from the measurements of the partition coefficient.

After this first part of the experiments, it was possible to conclude that both drugs could be absorbed after a rectal administration. But their great lipophilic affinity might cause an irregular bioavailability, especially for clomipramine. Such variations of bioavailability were reported previously by Luskombe with oral administration of clomipramine chlorhydrate (1).

GALENIC FORMULATION

Preparation of suppositories

The dosage of imipramine chlorhydrate or clomipramine chlorhydrate was 75 mg for 2 g suppositories, in accord with the usual oral dosages of these drugs.

The suppositories were prepared by melting the suppository bases and adding the drug to the liquid. They were solidified by cooling at 4°C.

A preliminary study showed that both drugs were insoluble in the excipients tested. They increased the melting temperature of the excipient of 1°C. Therefore the excipients were chosen among those which have a low melting point. They were selected from Witepols$^{(R)}$, and Suppocires$^{(R)}$ to have a large range of hydroxyl index.

Each batch was submitted to a 30°C storage for seven days to avoid a possible polymorphism of the half-glycerides.

Physicochemical tests

Only clomipramine chlorhydrate was used for all the assays of formulation with the seven chosen excipients. Every formula underwent all the physicochemical tests so that the best excipient was selected. The same excipient was used with imipramine chlorhydrate to obtain comparable formulae for further assays of bioavailability. The formulae reported in table 1 were submitted to the following assays :

- The rheological behaviour was measured, after melting at 40°C, with a rotative viscometer (Rheomat 30, Contraves, Zurich), at 37°C. All the formulae had a newtonian behaviour, just after manufacturing and also after the storage.
- The melting points were measured by the "U" tube method. They were below or equal to 37°C, just after manufacturing. They increased after the storage and the batches with Witepols H5, H15 and H25, and with Suppocire A were unacceptable.
- The liquefaction time was determined with the Krowczynski's technique, according to the Polish Pharmacopoeia method, which requires a maximum time of 15 minutes (4). All the data were below or equal to this value when the measurements are carried out after manufacturing, but after the storage liquefaction times smaller than 15 minutes were only obtained with suppocires.
- The disintegration time was measured by the Munzel's method, with an automatic apparatus (Erweka), according to the European Pharmacopoeia. All the results wer fit with the Pharmacopoeia's requirements. No significant

Table 1: Formulae and assays of the suppositories of clomipramine chlorhydrate.

Formulae: 75 mg of clomipramine chlorhydrate in 2 g halfsynthetic glycerides

	Witepsols			Suppocires			
	H 5	H 15	W 35	AIM	NAI 10	A	AP
Hydroxyle Index	5	15	30	6	15	20-30	30-50
Melting point (°C)	34-35	33,5-35,5	33,5-35,5	33-35	33,5-35,5	35-36,5	33-35
Assays of suppositories (means of 5 values) 1 : after manufacturing ; 2 : after 7 days of storage at 30°C							
	Melting point (°C)						
Assay 1	36.3±0.5	35.6±0.4	35.5±0.4	35.8±0.5	33.5±0.2	37 ±0.2	35.2±0.5
Assay 2	37.3±0.7	37.1±0.5	37.2±0.5	36.3±0.3	34.9±0.4	38 ±0.5	36.5±0.5
	Liquefaction time (minutes)						
Assay 1	15 ± 1	12 ± 2	13 ± 1	10 ± 2	10 ± 1	9 ± 1	7 ± 1
Assay 2	30 ± 2	25 ± 2	21 ± 3	10 ± 2	10 ± 2	11 ± 1	7 ± 1
	Disintegration time (minutes)						
Assay 1	10 ± 2	8 ± 1	6 ± 2	6 ± 1	8 ± 2	11 ± 2	5 ± 1
Assay 2	11 ± 2	9 ± 1	10 ± 1	7 ± 1	9 ± 2	17 ± 3	5 ± 1
	Spreading area (mm²)						
Assay 1	95 ± 5	190±10	145± 8	500±12	480±11	190± 7	418±12
Assay 2	8 ± 1	2± 0.5	2± 0.5	88± 8	265±10	52± 5	331±12
	Hardness (daN)						
Assay 1	> 5.4	> 5.4	> 5.4	5.4±0.2	> 5.4	5.2±0.2	5.0±0.2
Assay 2	> 5.4	5.4±0.8	> 5.4	2.4±0.2	> 5.4	2.8±0.2	1.4±0.2

quefaction and disintegration times and a newtonian behaviour after melting in order to increase the patient observance. The spreading area would be as large as possible to increase the contact area between the melted suppository and the rectal mucosa. Among the formulae which were selected in accord to these requirements, the suppocire NAI 10 was chosen for its better kinetic of release.

One batch, manufactured with Imipramine chlorhydrate and suppocire NAI 10, gave results similar to those

Table 2 : Kinetic of release of clomipramine chlorhydrate from suppositories (means of 5 assays).

	Witepsols			Suppocires		
	H5	H15	W15	AIM	NAI 10	AP
$T_{50\%}$ (min)	7 ± 1	7 ± 2	8 ± 1	6 ± 2	< 5	11 ± 2
$T_{75\%}$ (min)	11 ± 2	10 ± 2	11 ± 2	10 ± 2	5 ± 2	15 ± 2
$T_{90\%}$ (min)	45 ± 3	40 ± 3	> 60	> 60	25 ± 3	53 ± 4

obtained with clomipramine chlorhydrate (Table 3 and Table 4).

The homogeneity of both final formulae was cheked by extraction of the drug from six suppositories by the mean of an heated (60°C) solution of HCl 0.005M in methanol. The extracts were analysed by UV spectrophotometry at 252 nm. The results were 70.4 ± 5.25 mg increase was observed after the storage.

- The spreading area was calculated according to the watch glass method (4). The highest results were obtained with the four suppocires before and after the storage. Such a decrease after storage has been frequently reported (5).
- The hardnesses were controlled by the resistances to crushing (Erweka SBT, Euraf, Paris). They were sufficient just after making, but decreased after the storage for formulae containing suppocires AIM, A and especially AP. (Table 1).
- The kinetics of release were measured with the rotating basket method (4). The dissolution assays were carried out at 36°5 ± 0.5° with purified water as the dissolution medium, simultaneously in six vessels. The mesh of the basket was 460 nm and the rotating speed was 60 rpm.

Table 3 : Formula and assays of the suppositories of Imipramine chlorhydrate (means of 5 values).

* 1 : after manufacturing ;
2 : after 7 days of storage at 30°C.

	Formula : 75 mg of Imipramine chlorhydrate in 2 g of Suppocire NAI 10	
	Assay 1*	Assay 2*
Melting point (°C)	34 ± 0.5	34.5 ± 0.5
Liquefaction time (min)	12 ± 2	12 ± 1
Disintegration time (min)	7 ± 1	9 ± 1
Spreading area (mm^2)	535 ±15	229 ±12
Hardness (daN)	> 5.4	5 ± 0.2

Table 4 : Kinetic of release of clomipramine (C) and imipramine (I) chlorhydrates from suppositories manufactured with Suppocire NAI 10. (means of 5 assays).

	$T_{50\%}$ (min)		$T_{65\%}$ (min)		$T_{90\%}$ (min)	
	C	I	C	I	C	I
After manufacturing	< 5	< 5	5 ± 2	6 ± 1	25 ± 5	8 ± 1
After storage	5 ± 1	5 ± 1	6 ± 1	7 ± 1	25 ± 2	9 ± 1

The samples, filtered through a polyethylene filter, were analysed by in a UV spectrophotometer at 252 nm (Bioblock, Strasbourg). The frequency of the measurements and the calculation were carried with a microcomputer (Apple II).

The quickest kinetic of release was obtained with the suppocire NAI 10, with which 90 % of the drug were dissolved after 15 minutes. The slowest one was obser-

ved with the suppocire A. No difference between the batches was observed with the other excipients : 65 to 75 % of the drug were dissolved after 15 minutes (Table 2).

At the end of this second part, it was possible to select the best formula for the further experiments. The best formula would present a melting point below 37°C, but not too low to allow the handling of suppositories without melting. It would have the smaller li- for clomipramine chlorhydrate, and 70.5 ± 4.63 mg for imipramine chlorhydrate.

The stability of the drugs in the final formulae was determined from the previous extracts, by thin layer chromatography. The assay was carried out with NF 254 Silica plates and chloroform (8 p)- methanol (1 p)- acetic acid (1p) as the migration solvent. These stability tests did not show any degradation of the drugs.

STUDY OF THE RELATIVE BIOAVAILABILITY

Determination in rabbits

The relative bioavailability was determined in rabbits, compared to an intravenous injection of a 25 mg/2 ml solution of clomipramine chlorhydrate solution (Anafranil(R), Ciba Geigy), or of imipramine chlorhydrate (Tofranil(R), Ciba Geigy).

Two hours before the beginning of the test, male albino rabbits, of an average weight of 2.50 ± 0.4 kg received a subcutaneous injection of 5 000 UI.kg^{-1} calcium heparinate. Then, 10 mg of the drug either under in intravenous injections, or in suppositories were administered. Blood samples were taken at 5, 10, 15, 30, 60, 90, 120, 150 and 180 minutes after the administrations. The plasma samples were analysed after centrifugation, with an immuno-enzymatic technique (Syva-Biomérieux, Rungis, France). (Figure 2).

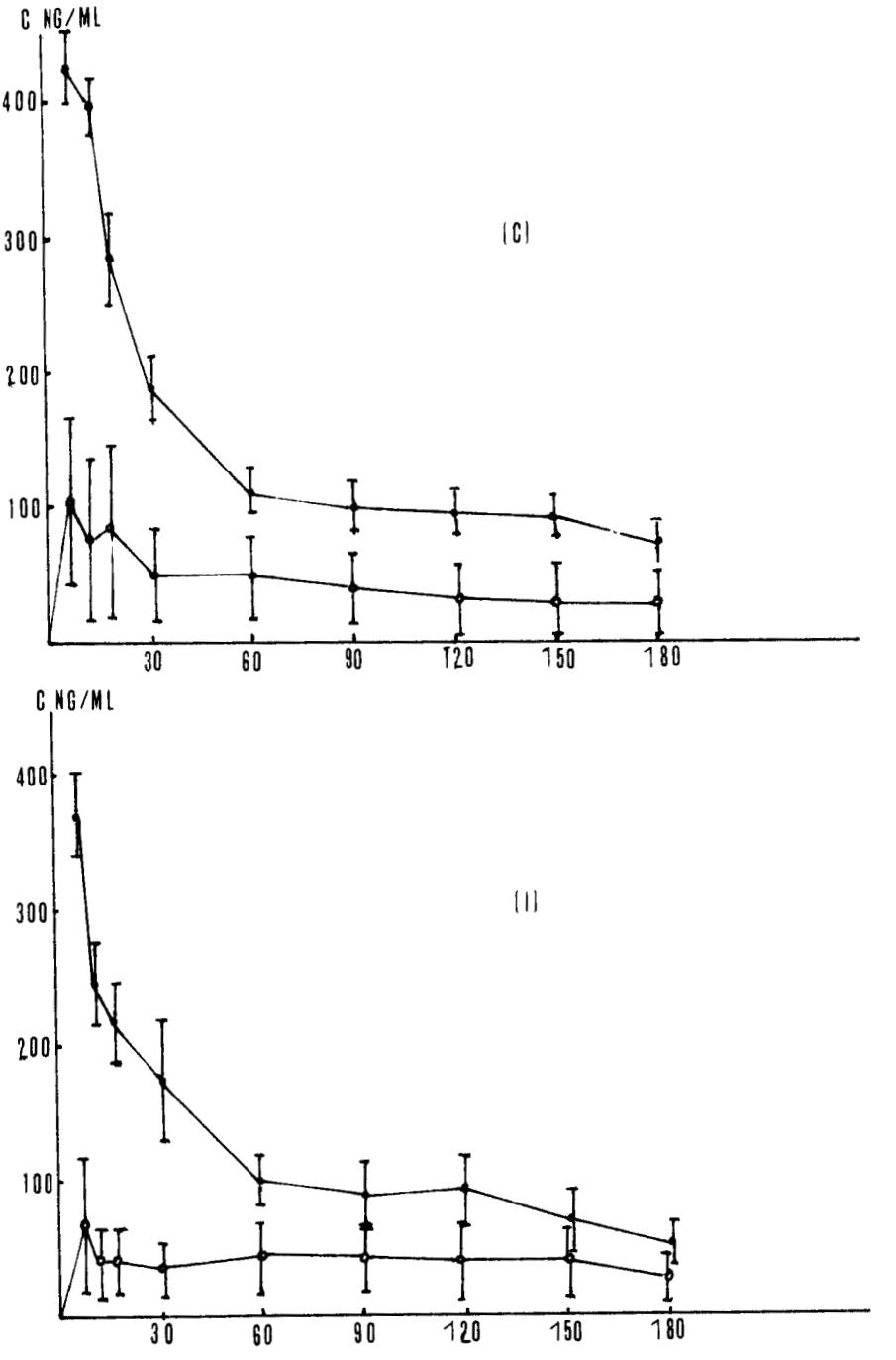

Figure 2 : Measurements of the plasmatic levels of clomipramine (C) and imipramine (I) in the rabbits after IV (●—●) and rectal (o—o) administrations of a 10 mg dose.

Table 5 : Protocole of the clinical assay.

	Patients		
Weight (kg)	62	54	42
Sexe	F	M	F
Age (years)	28	28	28
	Duration of treatment (days)		
1 suppository at 9h30	36	15	0
2 suppositories at 9h30 and 12 h	27	0	30
Blood samples every three days at 11 h 30			

The results showed that both drugs were rapidly absorbed by the rectal way. The relative bioavailability of the suppositories compared to the intravenous injections, were 28 % for clomipramine and 25 % for imipramine. These experiments confirm that clomipramine and imipramine could be absorbed by the rectal mucosa. Clinical assays were carried out with the suppositories even though the relative bioavailability seemed weak compared to the oral human bioavailability which is between 30 and 80 % (1).

Clinical assay

A clinical assay was carried out with suppositories containing clomipramine chlorhydrate on three inpatients at Saint Louis hospital in Paris, according to the therapeutic protocol reprint in table 5.

- First patient : this patient received 75 mg of the drug daily. The plasmatic level remained between 25 and 27 ng/ml during the first two weeks, and increased

Table 6 : Plasmatic levels (µg/ml) of clomipramine of patients treated with a 75 mg dose daily.

Days	3	6	9	12	15	18	21
Patient n°1	27	26	26	25	27	30	34
Patient n°2	52	54	70	40	60		

Table 7 : Plasmatic levels (µg/ml) of Clomipramine of patients treated with a double dose (2 x 75 mg) daily.

Days	35	40	45	50	60
Patient n°1	36	37	38	38	54
Days	16	19	22	25	30
Patient n°3	50	55	55	58	58

during the third week to 34 ng/ml. The doubling of the dosage for reason of therapeutic inefficiency increases the plasmatic level up to 54 ng/ml (Tables 6 and 7).

- Second patient with a 75 mg dose (Table 6), the plasmatic levels are higher than those of the first patient but not constant. The treatment was stopped after two weeks for that reason.
- Third patient : the third patient was treated with two suppositories since the beginning of the treatment. His plasmatic levels were measured between the 16th day and the 30th day of the treatment (Table 7). They stay between 50 and 58 mg/ml. The therapeutic efficiency observed with this patient was better than with the two others.

During this small clinical assay, the rectal tolerance of the suppositories was good.
The plasmatic levels, observed with patients treated with clomipramine chlorhydrate suppositories were slightly smaller than those obtained by Luskombe (1), and Burrow (6) with oral administrations of the same doses. The therapeutic efficiency was in the same range as after oral administration of tablets (7).

CONCLUSION

This study was carried out to define the conditions of the formulation of suppositories with clomipramine and imipramine chlorhydrates and the parameters of the absorption of these antidepressants in the rectal tract The formulae selected showed a satifactory bioavailability, comparing to oral forms. It would then be interesting to manufacture these antidepressants under a suppository form.

REFERENCES

1. Luskombe D.K., Brit. J. Clin. Pract., suppl. 3, 35 (1979).
2. Decroix M.O. "Contribution à l'étude biopharmaceutique des céphalosporines", Doctorat d'Etat ès Sciences Pharmaceutiques, Paris V, 1985.
3. Stricker H., Pharm. Techn., 31, 794 (1969).
4. Zuber M., Pellion B., S.T.P. Pharma, 3, 583 (1987).
5. Zuber M., Pellion B., Arnaud P., Chaumeil J.C., Int. J. Pharmaceutics, to be published.
6. Burrow D., Davies B., Norman T., Maguire K., Commun. Psychopharmacol., 2, 393 (1978).
7. Vandel B., Vandel S., Jonet J.M., Allers G., L'encéphale, 7, 601 (1981).