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Clomipramine test: serum level determination in three groups of psychiatric patients*

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Abstract: Concentrations of clomipramine, a specific and potent serotonin uptake inhibitor, are measured in 67 psychiatric patients and 12 normal volunteers. The psychiatric patients are grouped according to the DSM III R criteria namely; pathological gamblers, obsessive compulsives and sufferers of panic disorders.

Before and 30, 60, 90 and 120 min after an intravenous infusion of the drug (12.5 mg in 10 min), serum samples are collected to evaluate the concentrations of cortisol, prolactine and growth hormone. Simultaneously the clomipramine concentration of these samples is determined and these results only are reported in this communication.

Very different drug concentrations are observed in individual patients receiving the same amount of drug, indicating a substantial inter-individual variability of drug metabolism.

No statistical differences (Newman–Keules test) between the clomipramine concentrations from the patients of the three psychiatric groups and the normal group are observed. Neither are statistical correlations observed when clomipramine concentrations from all individuals (n = 79) are related with the age, sex or consumer behaviour (cigarette smoking, alcohol and coffee intakes) of the patients.

Keywords: *Clomipramine; psychiatric disorders; serotonergic uptake; drug administration.*

Introduction

Serotonin has an important role as a neurotransmitter in central nervous system regulatory processes. Alterations of serotonergic activity have been related with various psychiatric diseases such as depression, obsessive–compulsive disorder, panic, bulimia, schizophrenia and aggressive behaviour [1, 2].

The serotonergic activity can be measured indirectly by hormonal secretion, cortisol, prolactine and growth hormone which is controlled by hypotalamic factors influenced by serotonine [3–5]. Recent pharmacological studies have reported that serotonergic reuptake blocking drugs, may be efficacious in the treatment of various psychiatric processes [6, 7]. Clomipramine is a selective and potent inhibitor of serotonine uptake with an active hepatic metabolite, desmethylclomipramine, that inhibits the norepinephrine uptake.

Clomipramine correctly administered to selected psychiatric patients may be used as a biological marker to study the central serotoninergic function. This drug was used in a clinical protocol of the Psychiatric Service of the authors' hospital, in three groups of patients, obsessive–compulsives, pathological gamblers and sufferers of panic disorders (classified according to the DSM III R criteria American Psychiatric Association [9]) and in normal volunteers as control group.

Materials and Methods

Patients

A total of 67 patients (aged 18–60) were included in the study. The patients were grouped according to the DSM III R criteria. Twenty one of them (7 males and 14 females) had panic disorder, 23 (8 males and 15 females) suffered obsessive–compulsive disorder and 23 patients (19 males and 4 females) were pathological gamblers according to the DSM III R scores [9]. Also, 12 normal controls (3 males and 9 females) who had not concurrent DSM III R Axis I diagnosis were included in the study. Informed consent to the participation in the study was obtained from each individual.

Clomipramine test

All subjects received complete physical and neurological examinations and their laboratory tests were normal. None of the patients had

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been treated with any drug in the 2 weeks prior to the study. All participants fasted and did not smoke for the 12 h prior to the study.

Infusions of 12.5 mg of clomipramine (Anafranyl, Geigy) diluted in 100 ml of saline serum were administered for 10 min to each patient. During this time the patients were relaxed and resting in the supine position.

Blood sampling

Blood (10 ml) was withdrawn into dry tubes, prior to the infusion and 30, 60, 90 and 120 min after the infusion. Within 1 h the blood was cooled, centrifuged and the serum stored at −20°C until analysis.

Determination of plasma concentrations

High-performance liquid chromatography was used for the determination of clorimipramine in serum. Determinations were performed by means of a System Gold HPLC chromatograph (Beckman Co.) with an Ultrasphere silica column (15 cm × 4.6 mm) and a mobile phase consisting of ethanol–acetonitrile–water–diethylamine (990:8:1.5:0.5, v/v/v/v). Sample clean up was according to that published by Wong and McCauley [10] except that isopropanol was used instead of isoamyl alcohol. Clomipramine and the internal standard (imipramine) were extracted from the alkaline serum with hexane–isopropanol (98:2, v/v), prior to injection into the chromatograph. The UV detection was at 214 and 254 nm to recognize possible interfering substances. Analysis was according to the normal internal standard method.

Results

Tables 1 and 2, respectively, show the medians of clomipramine concentrations and the standard deviations obtained for all individuals (males, females and total) and for the different groups studied. The clomipramine concentrates decrease with the time elapsed after infusion and also, as might be expected, the results were low due to the length of the time passed from the start of the infusion (this was matched by the protocol study because the changes induced in the secretion of the hormone concentrations by the drug effect were measured at those times).

Table 1
Clomipramine concentrations (ng ml^{-1}) according to the sex of patients and time post-infusion

Time (min)	Males (n = 43)	Females (n = 36)	Total (n = 79)
30	54.54 ± 100.67	28.05 ± 43.77	42.47 ± 80.58
60	20.38 ± 28.70	16.65 ± 22.35	18.68 ± 25.91
90	13.44 ± 17.43	13.31 ± 18.00	13.38 ± 17.58
120	10.99 ± 14.45	11.52 ± 16.10	11.23 ± 15.12

Table 3 shows the mean age and sex of the patients and Table 4 the consumer behaviour of the patients. Figure 1 shows the time course of the medians of the clomipramine concentrations for the three psychiatric groups studied and the normal volunteer group. A different drop in the clomipramine concentrations can be seen for the distinct groups. The slopes appear not to keep any relationship with sex or consumer behaviour of the patients. It was observed that the group with the highest clomipramine concentrations had the highest mean age (see Tables 2 and 3).

Conclusions

The following conclusions may be drawn from the present study:

Table 2
Clomipramine concentrations* (ng ml^{-1}) by the groups studied

Group	Time post-infusion (min)			
	30	60	90	120
Pathological gamblers (n = 23)	54.51 ± 57.22	23.93 ± 25.85	15.57 ± 15.28	13.66 ± 16.64
Obsessive–compulsive disorder (n = 23)	43.07 ± 120.70	20.83 ± 29.37	14.59 ± 13.82	13.62 ± 13.71
Panic disorder (n = 21)	28.98 ± 49.72	11.87 ± 16.31	10.59 ± 18.42	7.02 ± 10.80
Healthy volunteers (n = 12)	41.85 ± 73.08	16.38 ± 32.44	11.75 ± 26.35	9.37 ± 20.45
Total (n = 79)	42.47 ± 80.58	18.68 ± 25.91	13.38 ± 17.58	11.23 ± 15.13

*Mean ± SD (SD = standard deviation).

Table 3
Sex and age of the patients

Group	Males (%)	Females (years)	Males (years)	Mean (years)
Pathological gambling (n = 23)	82	38.25 ± 8.70	41.30 ± 10.70	41.17 ± 9.93
Obsessive–compulsive disorder (n = 23)	35	33.10 ± 11.15	31.37 ± 13.04	32.52 ± 11.57
Panic disorder (n = 21)	33	35.06 ± 6.80	26.85 ± 5.08	32.45 ± 7.34
Norm controls (n = 12)	75	25.66 ± 3.70	27.41 ± 1.20	27.00 ± 2.08

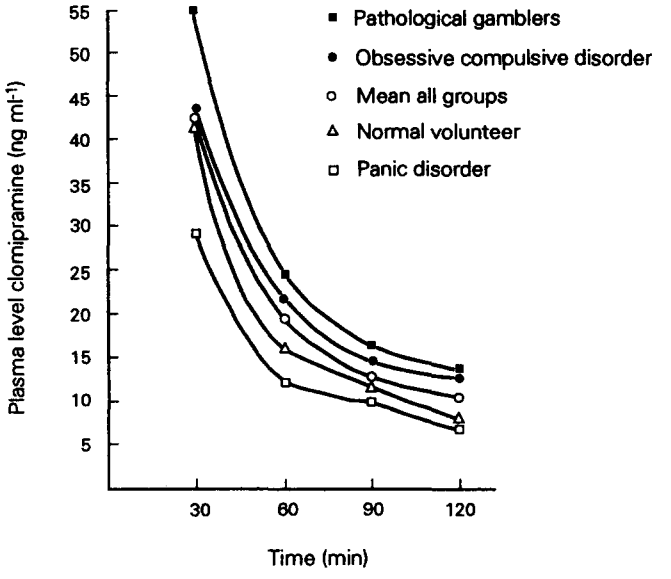

Figure 1
Clomipramine concentrations vs time post-infusion for each group studied.

Table 4
Consumer behaviour of the patients (n = 79)

Smoking (More than 10 cigarettes/day)	25%
Alcohol intake (1 l of wine or equivalent/day)	15%
Coffee (More than four cups of coffee/day)	32%

(i) Despite the direct administration (intravenous) of the drug, important variations of the clomipramine concentrations are observed during the period of time over which the sample testing was conducted. This is in agreement with the wide variations of the clearance reported for clomipramine for the same dose administered, due to endogenous factors (metabolic phenotype, hepatic blood flow and protein binding) of different individuals [10–12].

(ii) When clomipramine values are related to patient age, sex, cigarettes, coffee and alcohol uptakes no obvious correlations emerge. This is consistent with the results of previous studies in which the influence of exogenous factors (e.g. smoking, dietary habits) and their effects on clomipramine and other antidepressants serum drug concentrations have been investigated [13–16]. The highest half-life for the drug imipramine found for old men [16]. Cigarette smoking appears to lower the clomipramine and other antidepressants serum concentrations by induction of hepatic metabolism [18–20], however, some authors did not find any changes [21–23].

(iii) The more common side-effects observed (anxiety and dizzyness) were found in the patients with the highest drug values. These effects did not evaluate for any score scale.

From these conclusions it is suggested that,

given the great inter-individual differences of the clomipramine concentrations, it might be informative if the endocrine or behaviour responses to the drug are evaluated to discover the individual serum drug concentrations. Obviously, if it is necessary to revoke the noradrenalinergic effect of the active metabolite (desmethyl clomipramine) the elected way is the direct one. Also, it is suggested that it might be useful, if the anticholinergic side-effects are evaluated.

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