Efficacy of clonidine and of methadone in the rapid detoxification of patients dependent on heroin

The efficacy of a rapid detoxification schedule (8 to 10 days) with clonidine or methadone was evaluated in 30 patients addicted to heroin. The dose of study drug was preestablished according to the subject's weight and the amount of opioid consumption, and the total daily dose was reduced by approximately 15% during the study. All subjects completed the detoxification program and stayed in the hospital for at least 12 days. Clonidine and methadone therapies proved to be highly effective. There was a marked reduction in anxiety during opioid detoxification, although subjects' experiences differed according to the drug used. On the day of discharge, subjects who had received methadone still had attenuated withdrawal symptoms, whereas there were no such symptoms in the clonidine group. Muscular aching, flatulence, and daily drowsiness were more common among subjects in the methadone group, while subjects in the clonidine group had more sleep disturbances and weeping. Syncopal episodes and bradycardia occurred more frequently in the clonidine group. (CLIN PHARMACOL THER 38:336-341, 1985.)

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Recent studies have established the effectiveness of clonidine, an α-adrenergic blocker, in suppressing the signs and symptoms of opioid withdrawal in methadone, heroin, and synthetic opioid addictions.[4,5,7,8,10,11] Clonidine induces rapid opioid detoxification in subjects receiving methadone maintenance and allows subjects addicted to methadone to begin a maintenance program with naltrexone directly.[2] Ginzburg[3] published a detailed review of the use of clonidine or lofexidine to detoxify from opioids. We used short therapy schedules of clonidine or methadone in a double-blind fashion to detoxify patients addicted to heroin.

METHODS

Our subjects were heroin addicts who had been hospitalized in the Detoxification Unit of our hospital before their admission to a Drug-Free Therapeutic Community. The study was carried out in a voluntary admission unit that accepts individuals under controlled inpatient conditions provided that at discharge, the individual will arrange his or her admission to a Therapeutic Community. In our six-bed unit, patients were treated for physical dependence and associated organic complications, and during the 2-week hospitalization period they received neither telephone calls nor visitors. A series of inpatient regulations including random supervision of urine specimens was established.

Our subjects were heroin addicts of either sex whose age ranged between 18 and 35 years and who fit the DSM-III criteria for opioid dependence. None of the 45 patients originally admitted to the study has psychopathologic antecedents before drug addiction; all were in good health with no signs of cardiovascular disease. Two groups of 15 patients who completed the detoxification program and who remained hospitalized for a minimum of 12 days were studied.

The study was conducted in a double-blind fashion. Subjects were informed that they would be receiving methadone with clonidine placebo or clonidine with methadone placebo, and that they would be opioid free by the end of the study. Six different therapy schedules

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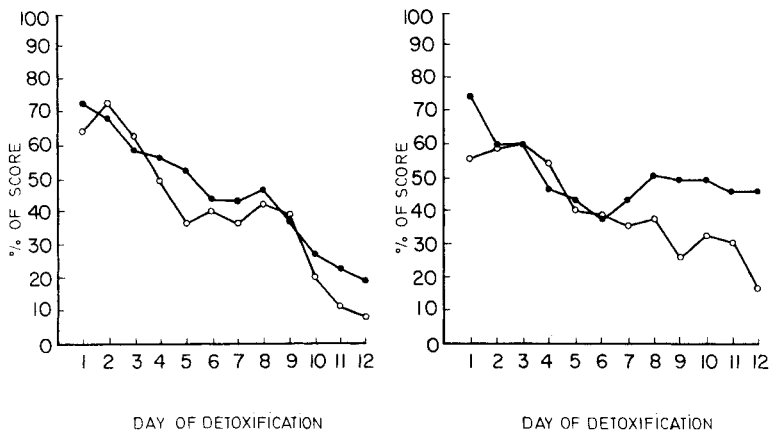

Fig. 1. Percentage of mean positive symptoms of withdrawal *(right)* and adverse effects *(left)* in the methadone (●) and clonidine (○) groups.

Table I. Dosing schedule

Subject weight (kg)	*Daily street heroin use during the last month (gm)*	*Initial daily dose (mg) at 8-hr intervals*	
		Clonidine	*Methadone*
≤55	≤0.25	0.90	30
≤55	>0.25 to <1	1.05	35
≤55	≥1	1.20	40
>55	≤0.25	1.05	35
>55	>0.25 to <1	1.20	40
>55	≥1	1.35	45

were preestablished according to the subject's weight and the amount of heroin consumed during the last month before study (Table I).

On treatment days 1 and 2, subjects received the same total dose (in fragments) at 8 AM and 4 and 12 PM. On day 3 and until discharge, the doses of clonidine and methadone were reduced (by 0.15 mg/day and 5 mg/day, respectively), with a tendency to decrease the afternoon dose first and then the morning dose, and finally the midnight dose. Placebo was given during the days of dose reduction and for 2 days after discontinuance of the drugs. Flunitrazepam, up to 4 mg, and acetylsalicylic acid, up to 2 gm, were prescribed for some subjects for nighttime sedation and analgesia. On the day of discharge (day 13 or 14), 0.4 mg naloxone was injected subcutaneously to evaluate residual withdrawal symptoms. The same team of three counsellors were responsible for the psychotherapeutic support of the subjects during the study.

A team of research nurses measured blood pressure,

Table II. Schedule for daily doses of clonidine and methadone

Detoxification day	*Clonidine (mg)*	*No. of subjects*	*Methadone (mg)*	*No. of subjects*
1*	0.780 ± 0.101	15	24.0 ± 3.4	15
2	1.083 ± 0.125	15	35.3 ± 6.4	15
3	0.960 ± 0.095	15	32.3 ± 6.5	15
4	0.810 ± 0.095	15	26.6 ± 4.0	15
5	0.664 ± 0.097	15	21.5 ± 3.5	15
6	0.510 ± 0.095	15	16.3 ± 2.9	15
7	0.360 ± 0.095	15	11.3 ± 2.9	15
8	0.210 ± 0.095	15	6.3 ± 2.9	15
9	0.180 ± 0.067	5	6.6 ± 2.8	3
10	0.150 ± 0.000	1	5.0 ± 0.0	1

Data are the $\bar{X}$ ± SD.
*Dosing began at 4 PM.

heart rate, and axillary temperature every day at 9 AM and 5 PM while the subjects lay in bed. The nurses completed daily abstinence rating scales recording the presence or absence of 19 signs associated with opioid withdrawal (craving, muscular aching, spontaneous ejaculation, insomnia, nightmares, hot/cold flashes, anxiety, restlessness, yawning, sweating, weeping, rhinorrhea, mydriasis, gooseflesh, tremors, anorexia, nausea, vomiting, and diarrhea) and 17 items related to adverse effects of the drugs (headache, mental clouding, asthenia, dizziness on standing, dry mouth, vertigo, buzzing, fatigue during walking, discomfort after ingestion, pyrosis, flatulence, salivation, hot flashes, generalized pruritus, visual abnormalities, daily drowsiness, and unstable walk). Subjects completed the State

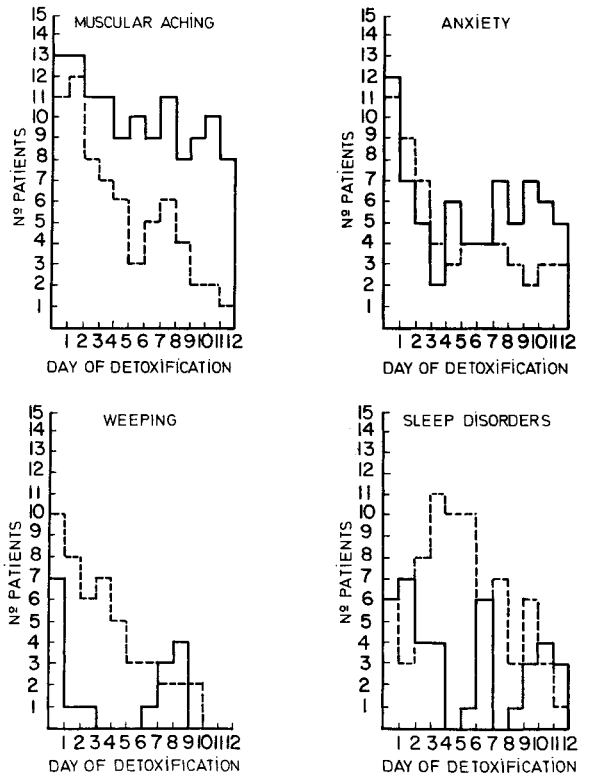

Fig. 2. Number of subjects with signs and symptoms of withdrawal during methadone *(solid line)* and clonidine *(dashed line)* therapy.

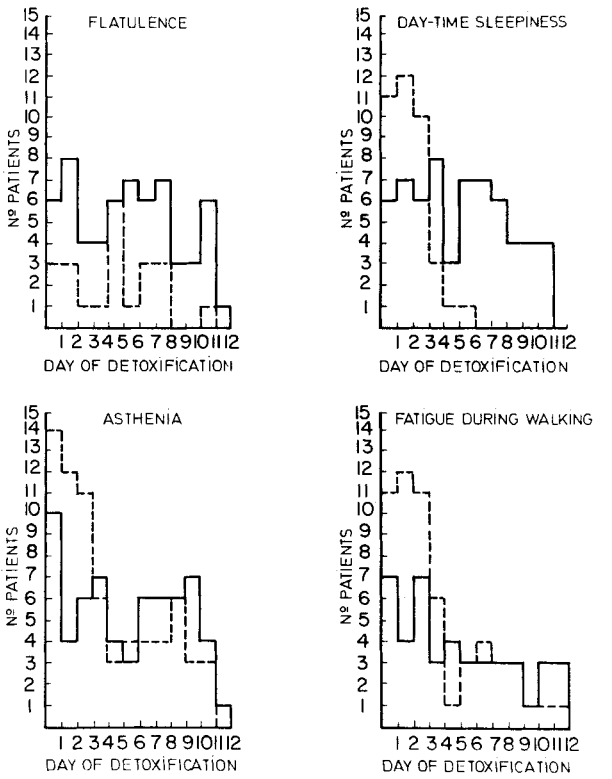

Fig. 3. Number of subjects with adverse effects attributed to methadone *(solid line)* and clonidine *(dashed line)* therapy.

Trait Anxiety Inventory questionnaire to measure state of anxiety[9] on treatment days 1, 2, 3, 4, 7, and 10 at 10 AM. Supervised urine specimens were collected daily for evidence of illicit drug use.

Results were assessed by ANOVA after logarithmic transformation of the original data. The Scheffé test was applied for mean comparisons. The Wilcoxon test and the median test with later application of the chi-square test and Yates correction were used in cases of nonparametric magnitudes. The maximum acceptable error was 5%.

RESULTS

Thirty of the 45 patients who began the study completed the therapy and were discharged drug free. Of the 30, 24 were men and six were women ranging in age from 18 to 30 years ($\bar{X}$ = 23.5 years). Subjects had a mean 4.2-year history of heroin consumption (range 1 to 10 years) and the mean number of previous supervised attempts to discontinue heroin was 1.8. Twelve patients decided that they did not want to continue with the research study and left before treatment day 10; three patients completed therapy after being shifted from the clonidine to the methadone group. Patients who failed to complete the study did not differ from the subjects with respect to previous attempts at detoxification and length of opioid dependence. Our final analysis applies to the 30 subjects (15 in the clonidine group and 15 in the methadone group) who completed the protocol. They were discharged from 12 to 17 days after admission ($\bar{X}$ = 13 days).

On treatment day 1, the initial clonidine dose of 0.78 mg and methadone dose of 24 mg were well tolerated. As shown in Table II, larger doses of drug were required on treatment days 2 and 3; after the first 3 days, however, clonidine and methadone dosage could be reduced (by 15%) and tapered without the recurrence of withdrawal symptoms on treatment day 9 in most subjects. Flunitrazepam was used preferentially by subjects in the clonidine group on the first and last days of detoxification, but the difference as compared with the methadone group was not significant. Acetylsalicylic acid was prescribed to relieve headache and toothache in nine subjects who received methadone and in seven who

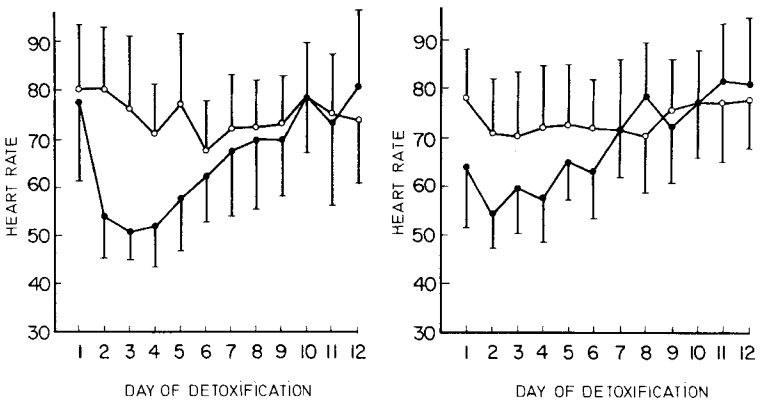

Fig. 4. Mean (±SD) changes in pulse rate at 9 AM *(left)* and 5 PM *(right)* in the clonidine (●) and methadone (○) groups.

received clonidine. On the morning of the day of discharge, 0.4 mg sc naloxone was given to all subjects to assess the extent of withdrawal signs.

The clonidine and methadone regimen we used was effective in rapid opioid detoxification. Fig. 1 shows the percentage of the mean number of abstinence and adverse effects rating scores reported daily. ANOVA showed a significant progressive decrease in the score along the days of detoxification ($F = 13.67$; $P < 0.001$). Although there were no significant differences between the groups, there were significant group-by-treatment day ($F = 3.82$; $P < 0.001$) and group-by-subjects ($F = 8.05$; $P < 0.001$) interactions. In the first half of the study there was a reduction in the score in the methadone group; in the second half, there was a greater reduction in the clonidine group. By the end of the study, withdrawal symptoms had practically disappeared in the clonidine group. An individualized analysis of the items on the withdrawal questionnaire (item/subject/day) revealed differences in some signs (Fig. 2). The subjects who received methadone had higher scores for muscular aching ($\chi^2 = 8.17$; $P < 0.01$) and anxiety ($\chi^2 = 4.17$; $P < 0.05$), whereas in the clonidine group the scores for weeping were higher ($\chi^2 = 6.04$; $P < 0.025$). There were no significant differences between the groups with respect to the remaining items.

In relation to the state of anxiety, ANOVA indicated a progressive decrease in the score along the days of treatment ($F = 11.12$; $P < 0.001$) and a group-by-treatment day interaction ($F = 2.36$; $P < 0.05$). There was a marked reduction in anxiety symptoms during the first days of therapy in the methadone group, whereas the reduction was more progressively constant throughout the treatment period in the clonidine group. In the methadone group, the only differences in daily scores corresponded to treatment days 7 and 12 as compared with treatment day 1; for the clonidine group there were differences between the scores on treatment day 12 and those on treatment days 1, 2, 3, and 4. The naloxone test did not reveal signs of interest in either of the groups.

There was a progressive decrease in the adverse effects rating score during the days of detoxification (Fig. 1), but there were no significant differences between both drugs with respect to days of treatment or to subjects in the groups. Analysis of each item on the adverse effects questionnaire (item/subject/day) revealed differences in some signs (Fig. 3). In the methadone group the scores were higher for flatulence ($\chi^2 = 4.69$; $P < 0.05$) and daily drowsiness ($\chi^2 = 6.04$; $P < 0.025$).

ANOVA of the effect of clonidine and methadone on supine systolic and diastolic blood pressures and heart rate indicated no differences in blood pressure between days, except for systolic blood pressure at 9 AM on treatment day 3 in the clonidine group ($F = 6.17$). During the study four subjects had orthostatic hypotension that was reversed with recumbency. One episode occurred on treatment day 7 in a subject receiving methadone, but there was doubt whether the fall in blood pressure was directly related to the drug. The three other episodes occurred on days 1 and 2 in subjects receiving clonidine. Systolic blood pressure was 50 mm Hg. There was a transient loss of consciousness in one subject receiving clonidine.

ANOVA of mean heart rates showed that at 9 AM and 5 PM there were significant differences between days ($P < 0.001$; in the clonidine group, between the first

5 and the last 5 days), between drugs ($P < 0.001$), and in the drug-by-treatment day interaction ($P < 0.001$). Comparison of mean heart rates for each day between the clonidine and methadone groups showed that for both drugs there was a difference at 9 AM on treatment days 2, 3, 4, and 5. Differences were also observed at 5 PM on treatment days 1, 2, 3, 4, 6, and 8 (Fig. 4).

DISCUSSION

In Spain, most of the therapeutic programs for opioid addicts are based on detoxification procedures followed by admittance to a Drug-Free Therapeutic Community. Methadone maintenance programs have been recently started because of legal regulations and their use is not established.[1] Our study was designed to compare the advantages and disadvantages of methadone and clonidine as agents of detoxification.

Clonidine or methadone therapy enabled 30 of 45 patients to be completely withdrawn from heroin addiction within 12 days after abrupt discontinuation of heroin. Eight of the 12 patients who requested to leave the Unit before treatment day 10 had started the protocol of detoxification with clonidine. Patients who failed to complete the study did not differ from the subjects with respect to previous attempts at detoxification and length of opioid dependence. One might speculate that clonidine precipitated some type of psychopathologic reaction[6] that resulted in a request for voluntary discontinuance of therapy.

The preestablished dosing schedules according to the subject's weight and heroin consumption allowed for maximum individualization of dosages while preserving the double-blind research design. We used these criteria because of the difficulty in ascertaining the seriousness of physical dependence.

Our results show that clonidine and methadone therapies made rapid opioid withdrawal possible, although the personal experiences of each subject differed for each drug. As indicated by the withdrawal rating scores, subjects receiving methadone had mild withdrawal symptoms at the end of the study, while subjects receiving clonidine appeared to be free of withdrawal signs and symptoms. The slowness in the decrease of the abstinence rating scale for the methadone group could be explained by eventual cumulation of the drug.

The adverse effects rating scores were similar in both groups and followed a curve related to the dose of drug. One of the aspects we most carefully considered was the differentiation between signs and symptoms attributable to adverse effects. Our results permit the documentation of the different sensations experienced by the subjects according to the drug used. Muscular aching was a frequent symptom of methadone withdrawal, whereas weeping was a frequent sign during clonidine withdrawal. Subjects receiving methadone had flatulence and daily drowsiness in a higher proportion than subjects in the clonidine group. The sedative effect of clonidine was much more prominent during the first 3 days of therapy. Subjects who received clonidine also had more sleep disturbances, usually manifest as early awakenings. If our protocol had included more subjects, these differences would have probably been more conclusive.

One of the main symptoms of opioid withdrawal is anxiety, a phenomenon difficult to evaluate objectively. Behavioral rating of anxiety recorded by the research nurses suggested the presence of this symptom more frequently in the methadone group. However, the self-rated STAI scale for anxiety completed by the subjects indicates an equal reduction in anxiety for both drugs as therapy progressed.

Clonidine had clinically important effects on blood pressure in three subjects on treatment days 1 and 2, despite the absence of significant differences in supine blood pressures at 9 AM and 5 PM. There were significant differences in the mean heart rates between the clonidine and the methadone groups. This was probably the main difficulty in the use of clonidine under the preestablished conditions of our study. Clonidine should be used in rapid opioid detoxification programs only by experienced personnel who can guarantee close surveillance, especially with respect to cardiovascular complications.

Our results indicate that the use of clonidine or methadone is effective in the treatment of heroin withdrawal syndrome, although symptoms presented by the subjects differed according to the drug used, whether we refer to the alleviation of the signs or symptoms of withdrawal or to the adverse effects related to each type of therapy. Further studies are needed to evaluate the distinct action of opioid substitutes and adrenergic agonists.

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