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Pharmacokinetic and pharmacodynamic characteristics of a controlled-release formulation of trazodone versus the conventional formulation in healthy volunteers

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The pharmacokinetic and pharmacodynamic characteristics of a controlled-release (CR) formulation of trazodone were evaluated in healthy subjects who received acutely 150 mg and 75 mg of the CR trazodone and equal amounts of the conventional formulation on separate occasions. Plasma trazodone concentrations were measured by HPLC. The pharmacokinetic profile of CR trazodone was characterized by a slower increase in drug plasma levels and a lower and retarded peak plasma concentration without any modification in the total amount of trazodone absorbed over 24 hrs. The side effects were less severe and less frequent than with the conventional formulation.

Key words: Pharmacokinetics — controlled-release trazodone — plasma levels.

Introduction

Trazodone is a non-tricyclic antidepressant drug with no anticholinergic activity [11], low levels of cardiotoxicity, low frequency of side effects at therapeutic doses [9, 10, 16] and a wide margin of safety in overdose [2]. These properties make trazodone an ideal antidepressant for use not only in geriatric depressed patients, who often do not tolerate anticholinergic side effects of tricyclic drugs, but also in general clinical practice, particularly at a time when the incidence of suicide or accidental poisoning is a real and growing concern [14].

The antidepressant efficacy of trazodone has been widely documented in several well controlled clinical trials [3, 6] and its side effects, of moderate intensity and of low frequency, seem to occur mainly when high doses are initially used or when the dosage is increased too rapidly [8]. The pharmacodynamic effects of trazodone appear to mirror the plasma concentration-time curve and so most untoward effects occur at the plasma peak concentration [4]. It therefore seems likely that side effects would be avoided if the early and relatively high peak plasma concentrations, of the conventional formulation, could be avoided with a new formulation of the drug. A controlled-release (CR) formulation of trazodone (Trittico AC, Angelini, Rome, Italy) has been developed. The aim of the present study was to evaluate pharmacodynamic effects and pharmacokinetic characteristics of CR trazodone compared to the conventional formulation. For this purpose, 75 mg and 150 mg of both conventional and CR trazodone were acutely administered p.o. in healthy subjects and the drug plasma levels and side effects were measured at different times after oral administration.

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Method

11 subjects (7 men and 4 women) volunteered for the study. They were within 15% of their ideal body weight and did not suffer from any medical illness as assessed by clinical interview and routine laboratory tests. Age range was 26-33 yrs (mean±SD = 29.8±2.9).
According to a randomized double blind design, each subject received orally 150 mg CR trazodone and 150 mg conventional trazodone on two separate occasions, one week apart. Experiments started in the morning after a conventional breakfast. Blood samples were collected immediately before and every hour over a 24-hour period after drug administration. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded every 30 min up to 8 hrs after drug administration. Side effects were assessed at baseline and after drug administration by checklist questioning for presence and severity of dizziness, headache, nausea, vomiting, palpitations, dry mouth, drowsiness, visual disturbance, tremor and fatigue. Side effects were scored on a 4-point scale ranging from 1 = low intensity to 4 = very severe.

5 of the 11 subjects (3 men and 2 women) volunteered for a second experiment. According to the above methodology, they received orally 75 mg CR trazodone and 75 mg conventional trazodone in two separate occasions, one week apart. Blood samples were collected at the same time points as above, except 18 hrs following drug administraion. Blood pressure and side effects were recorded.
Blood was collected in glass tubes with EDTA as anticoagulant. Plasma was separated by centrifugation at 3000 rpm and stored at - 20 °C until assayed for plasma trazodone levels, according to the following procedure. Each plasma sample (2 ml) was extracted by 5 ml n-hexane/isoamyl alcohol (v/v). After centrifugation at 3000 g for 3 min, the organic phase was recovered and dried under nitrogen flow. Each sample was reconstituted by 200 µl of elution buffer (1% TEA pH 3.0/acetonitrile 75:25). Plasma trazodone concentrations were determined by high-pressure liquid chromatography (HPLC) using a Beckman Ultrasphere ODS column 5 µl (mm 4.6×25 cm). Detection procedure was carried out at 314 nm by UV Beckman 163 variable wavelength detector

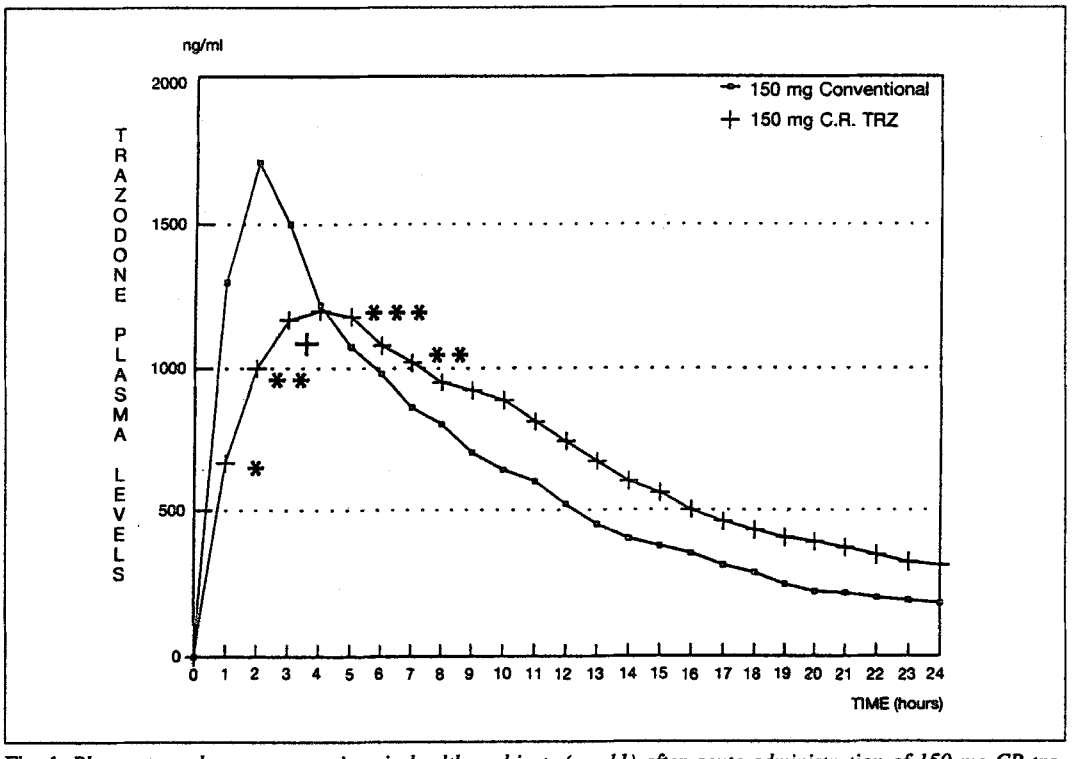

Fig. 1 *Plasma trazodone concentrations in healthy subjects (n = 11) after acute administration of 150 mg CR trazodone and 150 mg conventional trazodone.*
* $p<0.03$; ** $p<0.01$; *** $p<0.009$; + $p<0.008$; (Student's t-test for paired data).

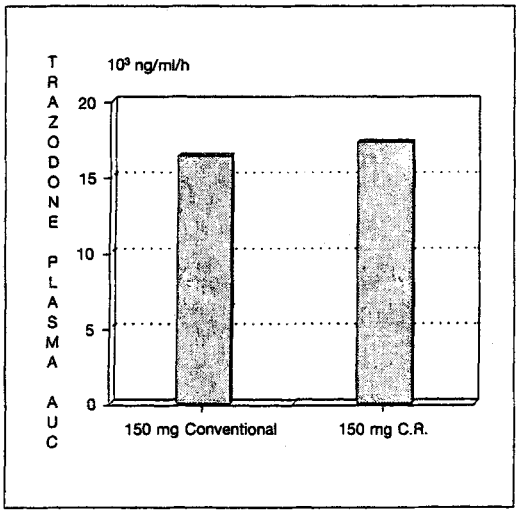

Fig. 2. *Areas under the curve (AUC) of plasma trazodone in healthy subjects (n=11) after acute administration of 150 mg CR trazodone and 150 mg conventional trazodone.*

(detection limit=10 ng/ml).
Results were expressed as mean ± SD and statistically analyzed by two-way analysis of variance (ANOVA) with repeated measures, Student's t-test for paired data, χ^2 test with Yate's correction and Pearson's product-moment correlation test, where appropriate.

Results

Oral administration of 150 mg conventional trazodone resulted in a peak plasma level of 1710±179 ng/ml 2 hrs later. The concentrations progressively decreased thereafter to reach about one half of the peak plasma concentration 7 hrs after drug ingestion (plasma half-life=7 hrs) (Fig. 1). Oral administration of 150 mg CR trazodone yielded a peak plasma concentration of 1200±389 ng/ml 4 hrs after ingestion and the plasma half-life was about 12 hrs (Fig. 1). Two-way ANOVA with repeated measures disclosed a significant drug X time interaction (F=5.22, P<0.00001), indicating a difference in the timing of plasma

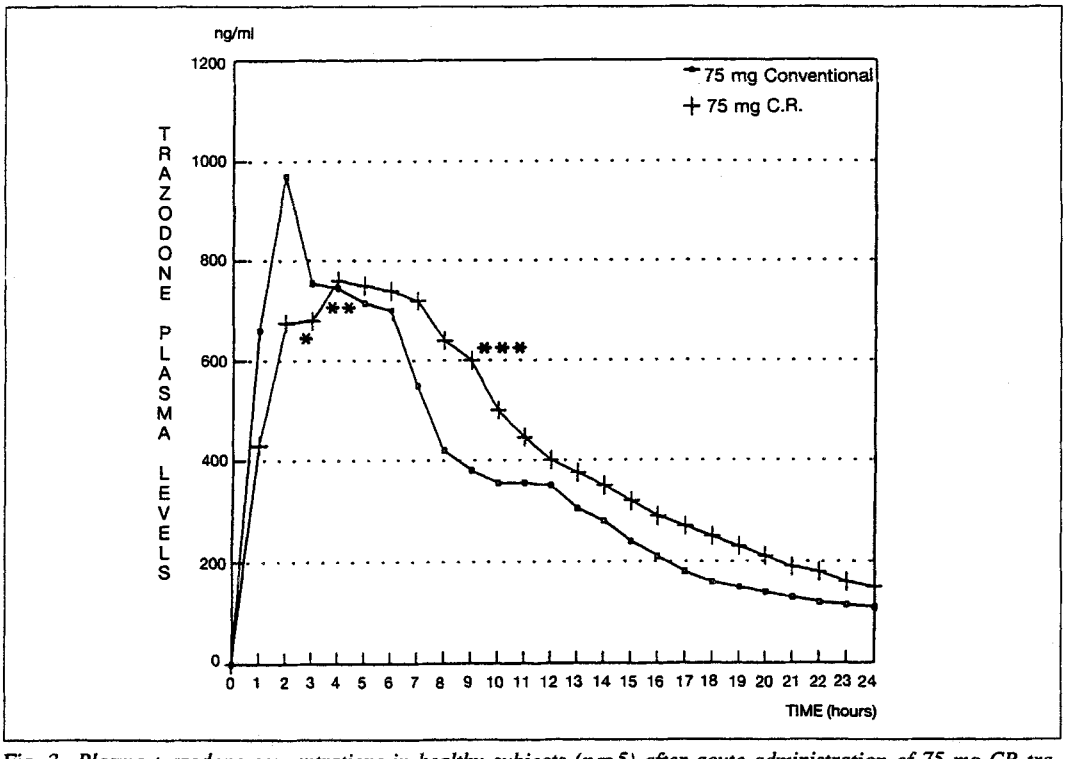

Fig. 3. *Plasma trazodone concentrations in healthy subjects (n=5) after acute administration of 75 mg CR trazodone and 75 mg conventional trazodone.*
** p<0.01; ** p<0.02; *** p<0.001; (Student's t-test for paired data).*

trazodone concentrations between the two drug formulations. Statistically significant differences at the various time points are indicated in Fig. 1. Although the pharmacokinetic profile of the CR formulation differed from that of the conventional drug, the areas under the curve (AUC) were not statistically different, indicating that there was no difference in the total amounts of trazodone absorbed after administration of the two formulations (Fig. 2).

Similar pharmacokinetic profiles were observed in the 5 volunteers who took 75 mg of trazodone in both the CR formulation and the conventional one (Fig. 3). Two-way ANOVA with repeated measures showed a significant drug X time interaction ($F = 1.66$, $p < 0.05$), indicating that the timing of plasma trazodone concentrations differed between the two drug formulations. No difference was observed in the AUC between the two formulations (Fig. 4).

After oral administration of 150 mg conventional trazodone SBP values decreased (Fig. 5). A significant inverse relation was found between plasma trazodone concentrations and SBP values ($r = -0.78$, $p < 0.002$), with the maximum SBP

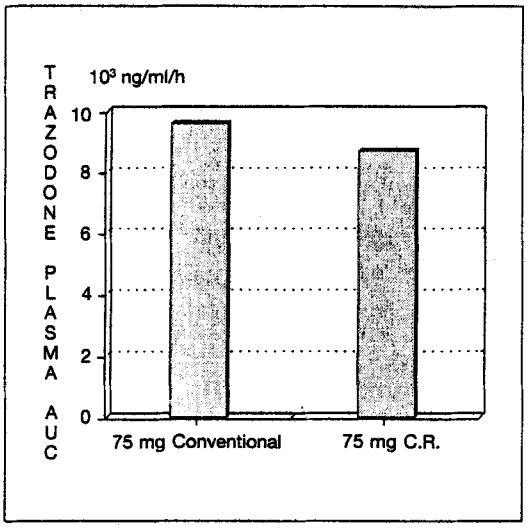

Fig. 4. *Areas under the curve (AUC) of plasma trazodone in healthy subjects (n = 5) after acute administration of 75 mg CR trazodone and 75 mg conventional trazodone.*

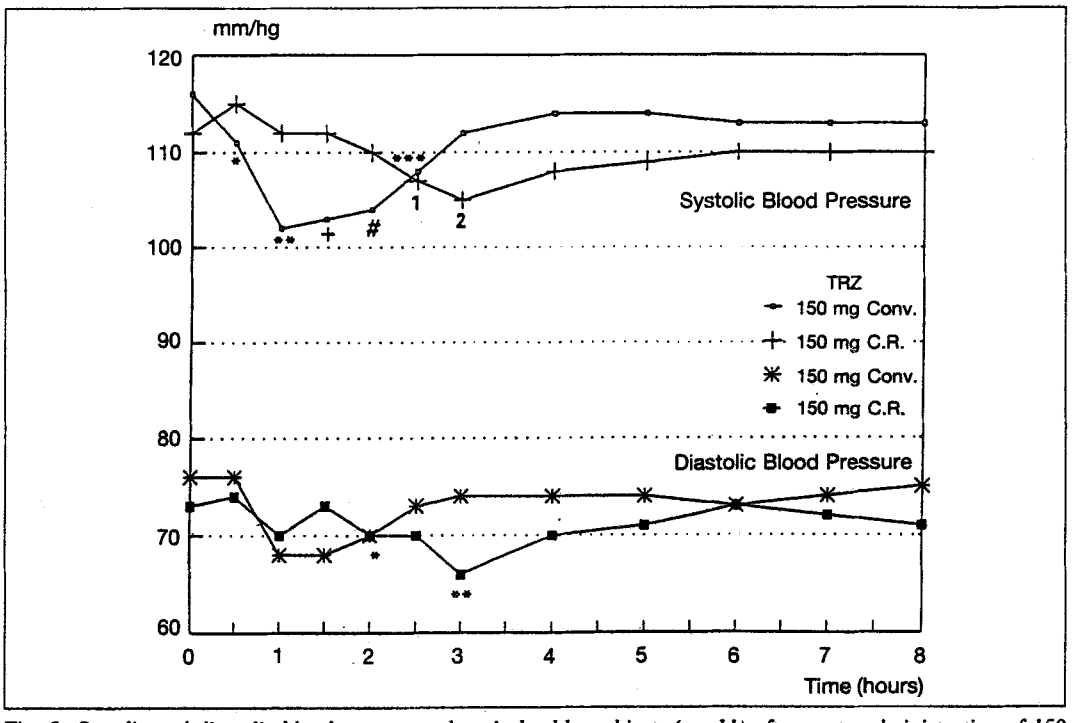

Fig. 5. *Systolic and diastolic blood pressure values in healthy subjects (n = 11) after acute administration of 150 mg CR trazodone and 150 mg conventional trazodone.*
*$p < 0.01$; **$p < 0.005$; ***$p < 0.003$; + $p < 0.0002$; # $p < 0.0000$; ¹ $p < 0.05$; ² $p < 0.009$; (versus corresponding basal values).

decrease occurring at the time of the plasma peak concentration of the drug (Fig. 5). Two subjects experienced orthostatic hypotension, immediately reversed by lying down.

After oral administration of 150 mg CR trazodone SBP values decreased and showed a significantly inverse relation with the plasma trazodone concentrations ($r = -0.61$, $p<0.02$). However, the SBP values fell significantly less than with the conventional formulation of trazodone (Fig. 5) and with no orthostatic hypotension in any subject.

DBP values showed a significantly inverse relation with the plasma trazodone concentrations ($r = -0.80$; $p<0.001$) only after administration of 150 mg conventional trazodone (Fig. 5).

No significant changes in SBP and DBP values were observed following oral administration of 75 mg trazodone in either formulation (Fig. 6).

Table I shows the number of subjects who experienced drowsiness of intensity ≥ 2 after trazodone administration. 2 and 3 hrs after ingestion of 150 mg conventional trazodone 7 subjects complained of drowsiness compared with none in the 150 mg CR trazodone group ($X^2 = 10.2$, $p<0.02$). In any case, in both treatment groups, drowsiness occurred at the times of peak plasma trazodone concentrations.

One volunteer in the 150 mg conventional trazodone group and two in the 150 mg CR trazodone group complained of nausea. Further side effects were: dry mouth (one subject treated with 75 mg conventional trazodone) and dizziness (one subject in the 150 mg conventional trazodone group).

Discussion

Our results clearly show a slower increase in drug plasma levels with the CR formulation than with conventional trazodone and a 20% decrease in the peak plasma concentration, which was shifted to two hrs later. This led to a prolongation of the plasma half-life (12 hrs of the CR formulation vs 7 hrs of the conventional one) and to a different pharmacokinetic profile of plasma trazodone without affecting the total amount of drug absorbed over 24 hrs.

In line with Abernethy et al. [1] and Spar [15], we found that after administration of both the conventional and the CR formulations of trazodone the drug reached plasma concentrations that

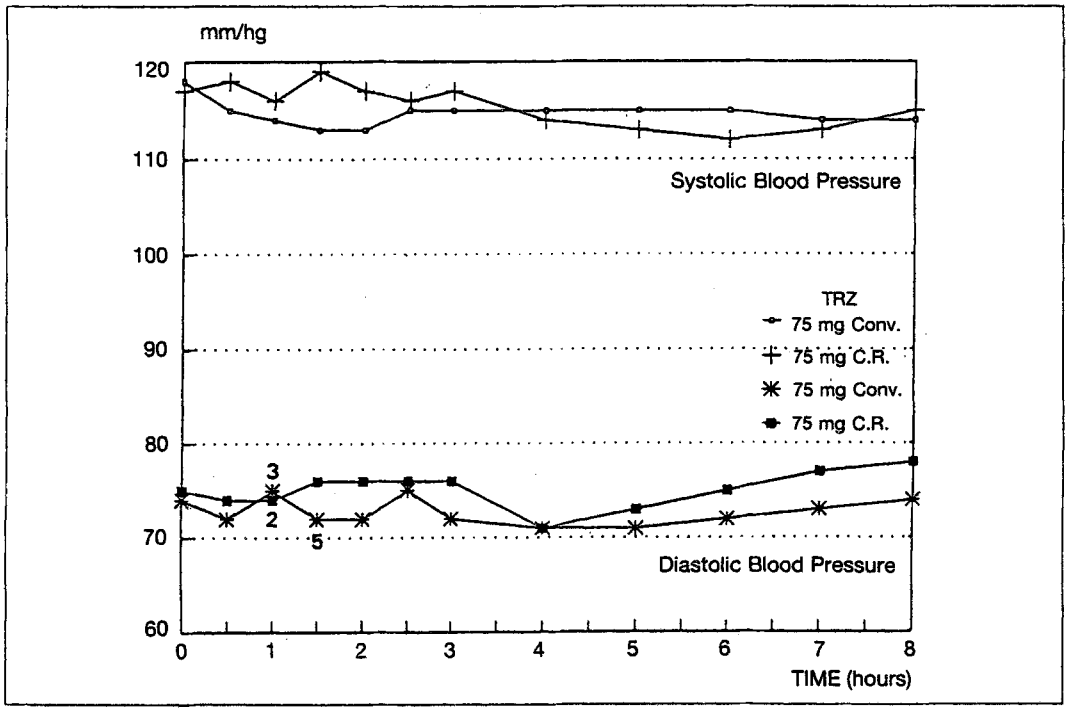

Fig. 6. *Systolic and diastolic blood pressure values in healthy subjects ($n = 5$) after acute administration of 75 mg CR trazodone and 75 mg conventional trazodone.*
[3] $p<0.04$; [4] $p<0.02$; [5] $p<0.002$ (versus corresponding basal values).

TABLE I. *Subjects who complained of drowsiness after oral administration of 150 mg trazodone in two different formulations.*

Time (hrs)	Conventional Formulation	CR Formulation	X^2	P
1.0	2	0	2.2	NS
2.0	7	0	10.2	0.001
3.0	7	0	10.2	0.001
4.0	5	3	0.7	NS
5.0	1	4	2.3	NS
6.0	1	4	2.3	NS
7.0	0	2	2.2	NS

CR = controlled-release.

were considerably higher than those usually attained by tricyclic antidepressants. Since we did not measure plasma concentrations of m-chlorophenylpiperazine (m-CPP), the main active metabolite of trazodone, we cannot exclude the possibility of different plasma levels of m-CPP with the two drug formulations. However, it has been reported that m-CPP does not reach appreciable plasma concentrations after single oral doses of conventional trazodone in man [7]. The measurement of plasma m-CPP levels might be more informative after long-term administration of the two formulations of trazodone.

In the present study side effects after the administration of 150 mg conventional trazodone were more frequent and more severe than after the same dose of CR trazodone and their occurrence was strictly and inversely related to plasma trazodone concentrations. These findings are consistent with those of Bayer et al [4], who showed that the pharmacodynamic effects of trazodone mirror the plasma concentration-time curve, and clearly demonstrate that flattening the peak plasma level of trazodone by the means of the CR formulation ensures a significant reduction in both frequency and severity of side effects, The same considerations may apply to the 75 mg dose od trazodone in both formulations.

It is not at present possible to say whether the different pharmacokinetics of the two trazodone formulations will result in different clinical outcomes in depressed patients. However, on the basis of the present results it is reasonable to suppose that the lower frequency of side effects in healthy volunteers attained by the CR formulation may improve the compliance of depressed subjects and result in more favorable outcomes. This hypothesis receives some support from a preliminary study showing no difference in antidepressant efficacy between CR trazodone and the conventional drug, with a lower frequency of side effects in the first week of treatment [5]. However, in Bayer's study [5], the lack of significant difference in the clinical outcome between patients treated with CR trazodone and those receiving equal amounts of conventional trazodone might be linked to inadequate plasma concentrations reached by the two formulations of trazodone. Indeed, we previously showed that a better clinical response is present in patients with steady-state plasma trazodone concentrations above 650 ng/ml [12, 13]. The different pharmacokinetic profiles of the two formulations of trazodone might account for different drug plasma levels at the steady-state even when patients are treated with the same daily dose. Further studies are needed to clarify this point.

In conclusion, the present results show that, independently of the dose, CR trazodone differs from the conventional formulation in pharmacokinetic profile and that at least in healthy volunteers, its side effects are less frequent and less severe.

Sommario

Le caratteristiche farmacocinetiche e farmacodinamiche di una formulazione di trazodone a rilascio controllato (CR) sono state studiate in volontari sani ai quali furono somministrati, in quattro differenti occasioni, 150 mg e 75 mg di trazodone CR e dosi equivalenti di trazodone in formulazione convenzionale. Le concentrazioni plasmatiche di trazodone furono misurate mediante HPLC. Rispetto alla formulazione convenzionale, il trazodone CR esibì un profilo farmacocinetico caratterizzato da un incremento più graduale dei livelli plasmatici e da una concentrazione massima più bassa e più ritardata. Nessuna differenza nella quantità totale di farmaco assorbita nelle 24 ore fu osservata tra le due formulazioni. Dopo somministrazione del trazodone CR, gli effetti collaterali indesiderati furono meno severi e meno frequenti rispetto alla formulazione convenzionale.

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