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Pharmacokinetics of trazodone and its major metabolite m-chlorophenylpiperazine in plasma and brain of rats

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Abstract

Sprague–Dawley rats were used as models for single trazodone administration (males), continuous administration and dose proportionality experiments (males, females, pregnant females). Plasma and brain tissue were analysed for trazodone and its active metabolite, m-chlorophenylpiperazine (m-CPP). Fetal exposure to trazodone and m-CPP was assessed and differences in their steady-state plasma concentration were sought between adult males and females. Both trazodone and m-CPP rapidly appeared in plasma and brain tissue following a single intraperitoneal trazodone dose with brain concentrations exceeding those in plasma. Plasma concentrations of m-CPP were lower than those of trazodone but exceeded them in brain tissue. Chronic administration using osmotic mini-pumps revealed a significant linear relationship between trazodone concentration in plasma and brain at steady-state ($r = 0.96$, $p < 0.0001$). No simple relationship was found between plasma and brain tissue concentration for m-CPP. In contrast to observations following single trazodone administration, m-CPP concentrations at steady-state were lower than trazodone concentrations in brain tissue, suggesting a lack of stationarity in the disposition of trazodone over time. No significant differences in plasma or brain tissue drug concentrations relative to administered trazodone dose were observed between male and female rats, nor between pregnant and non-pregnant females. Trazodone and m-CPP were both detected in fetal and placental tissues, with placenta having the highest concentrations. The data suggest that neuropharmacological studies of trazodone could yield different results depending upon the route and schedule of drug administration. Maternally administered trazodone, like many other antidepressants, is distributed to fetal tissues in rodents, reaffirming the need for caution in treating pregnant women with psychoactive drugs.

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Key words: m-chlorophenylpiperazine (m-CPP), mini-osmotic pumps, pharmacokinetics, placental transfer, pregnancy, serotonin, trazodone.

Introduction

Trazodone hydrochloride is a triazolopyridine derivative possessing antidepressant and possibly antianxiety activity. It differs from other major classes of antidepressant agents in several respects, including structure, pharmacology, and toxicity (Brogden et al., 1981). Trazodone was the first of the 'atypical' antidepressants to find widespread use in the United States and Europe. Major depression is the principal indication for the clinical use of

trazodone. It is commonly used in combination with selective serotonin reuptake inhibitors to provide night-time sedation.

In defining the preclinical pharmacology of this drug, Maj et al. (1979) found single trazodone administration to rats produced the pharmacological effects of a serotonin antagonist at low doses, while at higher doses, it possessed direct receptor agonist properties. Subsequent studies suggested that the latter effect was due to the actions of 1-m-chlorophenylpiperazine (m-CPP) rather than a dual action attributable to trazodone alone (Cervo et al., 1981; Melzacka et al., 1979). This metabolite is the result of hydrolysis and oxidation occurring on the side-chain of the parent compound (Caccia et al., 1981a, 1982; Melzacka et al., 1979). It is also a minor metabolite of the antidepressants etoperidone, mepiprazole and nefazodone

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(Barbhaiya et al., 1996; Fong et al., 1982a). The formation of m-CPP from trazodone in humans appears to be mediated by cytochrome P₄₅₀ (CYP) 3A4 (Rotzinger et al., 1998) which in turn can be further biotransformed to p-hydroxy-m-CPP by CYP2D6 (Barbhaiya et al., 1996). There is little information on which specific CYP isoforms are responsible for m-CPP formation in the rat.

Basic pharmacokinetic studies of trazodone have been carried out in normal human volunteers using single doses (Ankier et al., 1981; Bayer et al., 1983; Caccia et al., 1982; Greenblatt et al., 1987) or following multiple doses in psychiatric patients (Allroy et al., 1978; Ishida et al., 1995; Lawlor et al., 1997; Nilsen et al., 1993). Our knowledge of the disposition of trazodone and particularly that of its active metabolite in brain tissue compared to plasma is limited. However, some animal studies have been carried out where, following oral administration of trazodone, m-CPP appeared in the rat brain at a concentration comparable to that found following pharmacologically and biochemically effective doses of m-CPP (Caccia et al., 1981b; Cervo et al., 1981; Smith and Suckow, 1985). In addition, the concentration both of the parent drug and metabolite in the brain was several times greater than that measured in plasma. The higher concentrations of trazodone in the brain compared to plasma probably also exist in humans as post-mortem analysis in overdose cases found trazodone brain:plasma ratios of 3.4 and 1.4 (Martin and Pounder, 1992). The data, together with the observation that the metabolite reaches measurable plasma concentrations in humans receiving trazodone (Ishida et al., 1995; Lawlor et al., 1997), suggest that m-CPP contributes directly to or interacts with trazodone in producing antidepressant, antianxiety or adverse effects.

We sought to further understand the pharmacokinetics of trazodone and m-CPP by following the concentrations in plasma and brain of rats after single and continuous trazodone administration. In addition, we also investigated whether there were any gender differences in trazodone or m-CPP disposition and assessed their placental transfer and distribution in the rat fetus.

Methods

Single dose administration

All animal experiments were approved by the local Institutional Animal Care and Usage Committee. Male Sprague–Dawley rats weighing between 125 and 150 g were used in this experiment. Each animal was administered 30 mg/kg of trazodone, calculated as free base, by intraperitoneal (i.p.) injection. Previous studies (Miller and DeVane, 1986) suggested that a dose of 30 mg/kg in rats would produce plasma concentrations similar to that seen

in man following single oral dose administration of 50 mg (Abernethy et al., 1984).

The time-course of trazodone and m-CPP concentrations in rat plasma and brain tissue from administration of trazodone was determined at eight timed intervals following drug administration: 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h. Five animals were sacrificed at each time-point. After ether anaesthesia, blood was obtained by cardiac puncture for collection of plasma. The animals were then immediately decapitated and their brains rapidly excised. The brains were weighed and stored at -20°C for subsequent analysis by high performance liquid chromatography (HPLC) as described below. Additional animals not treated with trazodone were sacrificed and processed in the same manner in order to obtain drug-free plasma and tissues for preparation of HPLC calibration curves.

Chronic administration

Six groups of animals, consisting of 6–8 animals per group, had osmotic mini-pumps (Alzet[®] Osmotic Pump, model 2ML1, Alza Corp., Palo Alto, CA) containing trazodone implanted into their peritoneal cavity by a procedure which has been previously described (DeVane and Laizure, 1986). Four groups of male rats weighing approximately the same as those in the single-dose experiment were used to assess trazodone and m-CPP concentrations in plasma and brain following continuous dosing; with each of the four groups receiving either 5, 10, 30 or 50 mg/kg per day trazodone (calculated as base). Two additional groups of female animals were also studied. Their pumps contained trazodone calculated to deliver a dose of 30 mg/kg per day. One group was not pregnant while the other group consisted of pregnant animals whose pregnancies were accurately timed by the observation of sperm in the vaginal lumen (day of insemination = day 0). All surgery for mini-pump implantation was performed on the same day. For the pregnant animals, this corresponded to day 15 or day 16 of their expected 21 d gestation period.

After the animals had recovered from surgery and had been treated for 4 d, a period of time estimated to exceed that required to achieve steady-state conditions, they were sacrificed in a manner similar to that described above for the single-dose experiment. The day of sacrifice corresponded to days 19 or 20 of gestation for the pregnant animals. As the animals were expected to gain weight during the period following surgery, they were weighed again immediately prior to sacrifice to calculate the final daily trazodone dose. Additional tissues were saved from pregnant animals for HPLC analysis: whole fetuses; fetal livers; fetal brains, and placental tissue. Each

tissue was immediately weighed, stored on dry ice, then frozen for subsequent analysis by HPLC. The procedure for tissue collection from pregnant animals has been previously described (DeVane and Simpkins, 1985).

Assay procedure

The validated HPLC method of Miller and DeVane (1986) was used for all analyses. Samples were analysed on the same day as collection. Brain, plasma and fetal tissue samples were prepared and extracted as previously described. Briefly, tissue samples were homogenized, each sample was then alkalinized with saturated sodium borate solution and extracted with methyl-tert-butyl ether. Samples were then back-extracted with phosphoric acid and an aliquot of the aqueous phase injected onto a reversed-phase C_1 column. A mobile phase of acetonitrile and phosphate buffer, pH 3.0, was used to elute the compounds of interest. Quantitation was performed by comparing peak height ratios of trazodone or m-CPP to an internal standard (200 ng bupropion hydrochloride) with ratios derived from a calibration curve of standards containing known amounts of drug and metabolite extracted from plasma or tissue as described above. An IBM chromatograph was used with detection by UV absorbance monitoring at 214 nm. Final concentrations of trazodone and m-CPP were expressed as either ng/ml for plasma or ng/g for brain and fetal tissues. The limit of detection was 1.0 ng/ml for both trazodone and m-CPP. The intra-day coefficient of variation (CV) for trazodone and m-CPP extracted from plasma and tissues was < 2.1 and $< 7.0\%$, respectively.

Data analysis

Pharmacokinetic parameters were determined by inspection of the empirical data. Half-lives were determined by least squares linear regression analysis of the log-transformed data points of the terminal slope from the single-dose experiment. Area under the curve (AUC) calculations were made using the trapezoidal rule.

For the continuous dosing experiment, a linear regression analysis was used to examine correlations between administered dose and the resulting plasma trazodone and m-CPP concentrations. Additional correlations were sought between trazodone plasma concentration as the independent variable and brain tissue trazodone and m-CPP concentrations as dependent variables. A one-way analysis of variance was used to test for differences in means of steady-state plasma concentrations, normalized for dose, between males, females and

pregnant females. The level of significance was set at $p = 0.05$. All data are quoted as mean \pm s.d. unless otherwise stated.

Results

Plasma and brain tissue concentrations of trazodone and m-CPP vs. time profile for the single-dose experiment are shown in Figure 1. Concentrations in plasma and brain were comparable to similar single oral doses of trazodone (Caccia et al., 1981b; Cervo et al., 1981). In our experiment, trazodone was rapidly absorbed and distributed extensively into brain tissue. In the first timed sample, at 0.5 h, concentrations of trazodone were at their maximum in all tissues examined. The ratio of trazodone concentration in brain tissue to that in plasma in the first sample was 6.0. Brain tissue m-CPP concentration exceeded plasma m-CPP concentration by a factor of 53. Except for the first sample, brain tissue concentrations of m-CPP always exceeded those of trazodone in the subsequent samples over the 6 h of the study. The single-dose pharmacokinetic parameters are summarized in Table 1.

Animals sacrificed after 4 d of continuous trazodone dosing were found to have lower concentrations of trazodone in brain tissue compared to those found in plasma, a situation in contrast to the single-dosing situation (Figure 1). For all chronically dosed animals with measurable concentrations of trazodone, the ratio of brain to plasma trazodone concentration was 0.53 ± 0.17 ($n = 35$), the mean dose of trazodone was 20.0 ± 13.5 mg/kg. In further contrast to the single-dose situation, brain tissue trazodone concentrations were higher than m-CPP con-

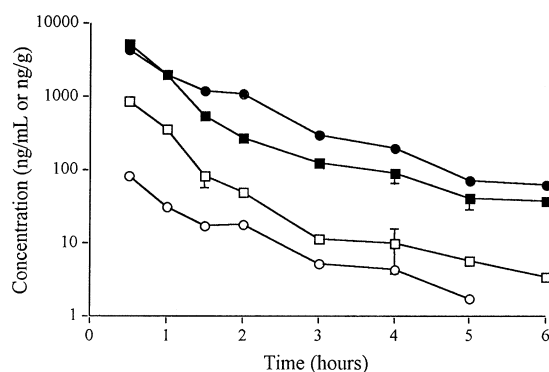
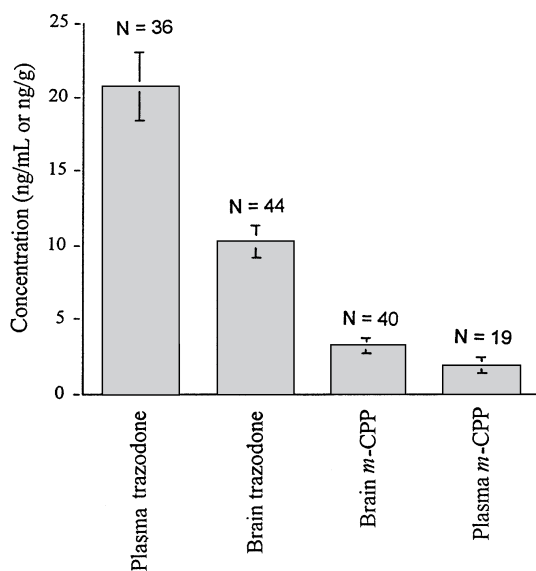


Figure 1. Concentration vs. time profile for m-CPP (circles) and trazodone (squares) in plasma (open symbols) and brain tissue (closed symbols) of male rats following a single intraperitoneal trazodone dose of 30 mg/kg. Each point represents the mean (\pm s.e.m.) of 4 or 5 animals. s.e.m.s not shown were smaller than the symbol size.

Table 1. Pharmacokinetic parameters for trazodone and m-CPP in rat plasma and brain following a single dose of 30 mg/kg of trazodone by the intraperitoneal route

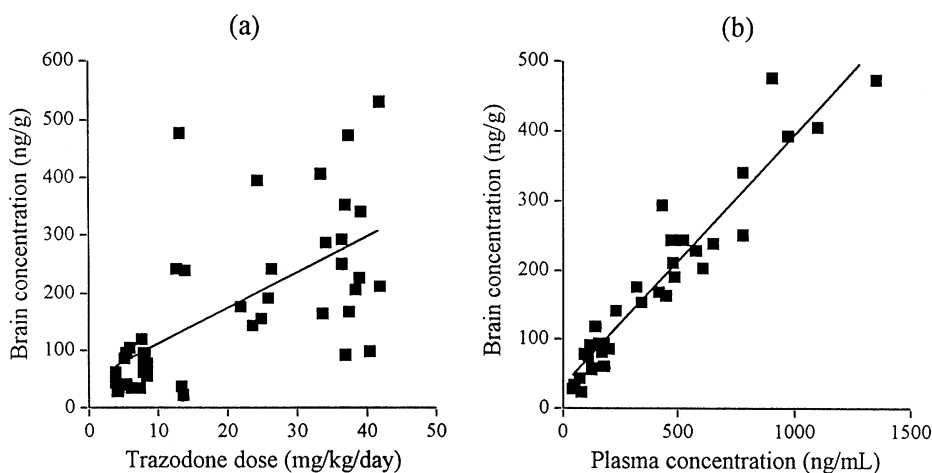
	Trazodone				m-CPP			
	t_{\max} (h)	C_{\max} (ng/ml or ng/g)*	$t_{1/2}$ (h)	AUC (ng/ml·h or ng/g·h)	t_{\max} (h)	C_{\max} (ng/ml or ng/g)*	Apparent $t_{1/2}$ (h)	AUC (ng/ml·h or ng/g·h)
Plasma	0.5	881 (209)	1.79	734	0.5	86 (17)	1.03	94
Brain	0.5	5262 (1043)	1.21	4419	0.5	4542 (964)	1.16	5376

* Data is mean (\pm s.e.m.), $n = 4$ or 5.

**Figure 2.** Mean (\pm s.e.m.) steady-state concentrations of trazodone and m-CPP in chronically dosed rats.

concentrations in all animals. The ratio of brain tissue trazodone concentration to brain tissue m-CPP concentration was 3.49 ± 2.50 ($n = 40$). In most animals, m-CPP was present in only trace amounts in plasma (< 5 ng/ml), while it was measurable in the brain tissue of all animals. Figure 2 shows the steady-state concentrations of trazodone and m-CPP in plasma and brain tissue for the continuous dose study.

The relationship between administered dose and resulting trazodone plasma concentration was significant but considerable variability was observed ($r = 0.68$, $p < 0.0001$). Other correlations between dose and resulting concentration of either drug or metabolite in plasma or brain were similar (range: $r = 0.64$ – 0.76). Using plasma trazodone concentration as the independent variable, a strong linear relationship existed with brain tissue trazodone concentration ($r = 0.96$, $p < 0.0001$). This relationship is shown in Figure 3 and is compared with the relationship between trazodone dose and its brain tissue concentration. No simple relationship was

**Figure 3.** Relationship in rats continuously dosed with trazodone between (a) dose and brain trazodone concentration ($n = 42$) and (b) plasma and brain trazodone concentrations ($n = 34$). Lines represent the linear regression lines of best fit.

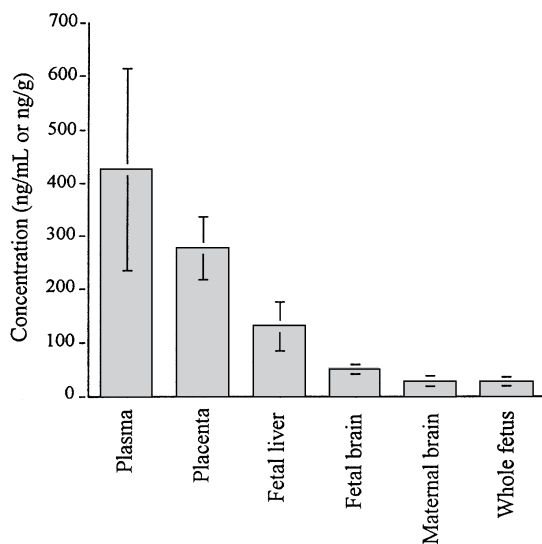


Figure 4. Mean (\pm S.E.M.) steady-state concentrations of trazodone in maternal plasma and tissues of pregnant rats and fetuses ($n = 5$).

observed between the concentration of m-CPP in plasma and that in brain ($r = 0.37$).

Because of differences in the final weight of chronically dosed animals at sacrifice compared to baseline before pump implantation, animals could not be strictly assigned to the original dose groups. Therefore, comparison of mean steady-state concentrations between males, females, and pregnant females was made by normalizing each animal's plasma concentration by their final mg/kg dose. No significant difference in mean steady-state plasma concentration for administered dose was found between males (mean \pm S.E.M., 17.6 ± 8.6 ng/ml per mg/kg, $n = 26$) and females (26.1 ± 5.65 ng/ml per mg/kg, $n = 5$) or between females and pregnant females (32.4 ± 14.1 ng/ml per mg/kg, $n = 5$).

Assay of fetal tissues for trazodone and m-CPP found measurable trazodone concentrations in all tissues examined. These results are shown in Figure 4. The order of concentrations from highest to lowest for trazodone was maternal plasma > placenta > fetal liver > fetal brain > whole fetus = maternal brain. m-CPP was present in relatively low concentration in the fetal tissues examined (< 25 ng/g of tissue).

Discussion

Experience with the tricyclic antidepressants and fluoxetine has shown that metabolites may be important in producing therapeutic and/or toxic response. m-CPP appeared rapidly in plasma following a single dose of trazodone (Figure 1). As the intraperitoneal route of administration is analogous to oral administration in

humans, these results suggest that m-CPP is formed by pre-systemic elimination (first-pass effect) in the liver and gut wall. In addition, m-CPP concentration was higher in brain tissue than plasma in both the single- and continuous-dose experiments. Measurable amounts of m-CPP in human plasma have been reported after single oral trazodone doses (Fong et al., 1982b; Ishida et al., 1995; Lawlor et al., 1997). Thus, brain concentrations of m-CPP formed from administered trazodone may reach therapeutically effective levels.

Of interest in our study was the paradoxically higher concentrations in the brain of m-CPP compared to trazodone following a single dose. This contrasts with lower concentrations of m-CPP than trazodone in plasma (Figure 1). m-CPP may be less tightly bound to plasma proteins than trazodone, thus allowing a greater amount of free drug to reach the site of action. m-CPP may bind more avidly to central nervous system tissue than trazodone. Plasma protein or tissue-binding studies of m-CPP have not yet been reported. An influx pump with different affinities for trazodone and m-CPP, which is down-regulated at steady-state, or changes in brain metabolism at steady-state, may also account for apparent high initial blood-brain barrier permeability.

This study found major differences in relative drug and metabolite concentrations in brain tissue following continuous dosing compared to the single-dose situation. While m-CPP concentrations were generally greater than trazodone in brain tissue following a single dose (Figure 1), at steady-state trazodone predominated over m-CPP in the brain (Figure 2). This was an unexpected finding that would not be predicted from the single-dose data. It is possible that during the accumulation to steady-state that the overall clearance of formed m-CPP changes and a greater proportion of the metabolite is eliminated over time. Alternatively, the clearance of trazodone might decline at steady-state. Rurak and Melzacka (1983) previously reported that trazodone concentration in the rat brain was lower after chronic dosing than from single-dose administration. Friedman and Cooper (1983) found evidence for altered disposition of desmethylclomipramine in rats when clomipramine was given repeatedly compared to a single dose.

The relevance of these observations for neuropharmacological studies is the suggestion that pharmacologic actions of antidepressants, especially those with active metabolites, may differ according to the route and time-course of administration. Other factors in experimental design of neuropharmacological studies are important. Aulakh et al. (1988) found that the neuroendocrine responses to the administration of m-CPP differed according to the strain of rat used experimentally. While we did not find significant differences between the mean

trazodone concentration in brains of male compared to female animals, there was a trend for higher concentrations per administered dose in the females.

We found a strong linear relationship existed between dose and the resulting trazodone brain concentration (Figure 3). Not surprisingly, a stronger correlation existed with plasma concentration and brain concentration. This probably reflects an equilibrium between the drug in the plasma and drug in the brain suggesting that a true steady-state existed due to the use of mini-osmotic pumps. These pumps are rate-controlled drug-delivery systems for implantation in laboratory animals. A major advantage of their use is that a constant-rate of drug input can be achieved, similar to a constant rate intravenous infusion. This avoids the necessity of daily drug dosing. Other advantages are simplicity of animal preparation and minimal animal stress following recovery from surgery. They have been used successfully in previous studies of neuroreceptor sensitivity changes and endocrine effects from chronic antidepressant therapy (Wozniak et al., 1989a,b); however, we cannot exclude the possibility that this method of drug administration influenced the kinetics of trazodone and m-CPP.

By analysing tissues for trazodone and m-CPP concentrations in pregnant animals, this study found that trazodone crossed the placenta and was distributed into the fetus of rats. However, the steady-state concentrations of trazodone were much lower in fetal tissue than in the maternal plasma. Only trace amounts of m-CPP were present in the fetus compared to trazodone. This finding contrasts with the results of experiments using other lipid soluble antidepressants. We previously found that imipramine, and its metabolite desipramine, were extensively distributed to rat fetal tissue from maternal plasma (DeVane and Simpkins, 1985). However, the apparent lesser degree of trazodone's transplacental distribution does not imply a greater safety of trazodone in pregnancy compared with imipramine. Drug effects on the fetus are determined by a number of factors, including the duration of drug exposure, gestational age of the fetus, and inherent pharmacological properties of the drug. These results demonstrate that trazodone, like other antidepressants, is capable of reaching the fetus following maternal drug administration (Calabrese et al., 1985).

In summary, these studies found that intraperitoneally administered trazodone to rats resulted in rapid appearance of trazodone and its major metabolite, m-CPP, in both plasma and brain tissue. While m-CPP was the predominant compound in the brain following a single dose, this finding did not hold for continuous dosing. This implies that trazodone's kinetic parameter may change with chronic administration. If replicated, this means that the results of single-dose studies in animals may not be

appropriate to extrapolate to the situation in man where antidepressants are usually administered continuously for several weeks or months. A linear relationship was apparent between plasma and brain concentrations of trazodone but no simple relationship was found for the metabolite. For trazodone, the results of the continuous administration experiments are likely to be of most experimental and clinical relevance. These findings suggest that future studies should carefully examine experimental strategies including acute vs. chronic kinetics and the relationships between drug and active metabolites that may account for pharmacologic effects.

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