Pharmaceutical Research, Vol. 4, No. 1, 1987

Research Article

N-(2-Cyanoethyl)tranylcypromine, a Potential Prodrug of Tranylcypromine: Its Disposition and Interaction with Catecholamine Neurotransmitters in Brain

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Received May 5, 1986; accepted August 18, 1986

The disposition of the *N*-cyanoethyl analogue of tranylcypromine (TCP) and the TCP formed from it have been studied in the rat brain following intraperitoneal (ip) administration (0.1 mmol/kg) and the resultant data compared with those obtained following an equimolar dose of TCP. Brain concentrations of the neurotransmitter amines dopamine (DA) and noradrenaline (NA) have also been determined, as well as the percentage inhibition of monoamine oxidase (MAO) types A and B. Our results indicate that the *N*-cyanoethyl analogue may be a useful prodrug of TCP, providing lower but more sustained concentrations of TCP in brain. Brain levels of DA were increased in a similar pattern after CE-TCP or TCP. Brain levels of NA were decreased by TCP at most time intervals, while CE-TCP produced a much less pronounced effect. Both CE-TCP and TCP inhibited MAO-A and MAO-B, with maximum inhibition occurring 60 min after CE-TCP dosing and 30 min after dosing with TCP, times at which brain concentrations of CE-TCP and TCP were at the maximum.

KEY WORDS: monoamine oxidase inhibitors; tranylcypromine; *N*-(2-cyanoethyl)tranylcypromine; catecholamines; brain; prodrug.

INTRODUCTION

In an ongoing project on prodrugs of bioactive amines, we have synthesized in our laboratories several N-alkylated analogues of tranylcypromine (TCP), a monoamine oxidase inhibitor. Tranylcypromine is a clinically used antidepressant (1) that has a relatively short elimination $t_{1/2}$ in serum (2). It has also been shown that although TCP reaches high levels in rat brain relatively soon after intraperitoneal administration, the drug also disappears rapidly from the brain (3,4). We have investigated the possibility of employing the *N*-cyanoethyl analogue (Fig. 1) as a potential prodrug to improve the pharmacokinetics of TCP. Improved bioavailability (5) and, in some cases, improved $t_{1/2}$ (6) have been reported for drug analogues that undergo metabolic biotransformations and liberate the active drug. The *N*-cyanoethyl analogue was considered for use since a similar analogue of amphetamine, *N*-(2-cyanoethyl)amphetamine, commonly known as fenproporex, is used clinically as an anorexiant (7–9). The *N*-cyanoethyl substituent has also been shown to be readily removed metabolically (10–12). We have therefore investigated the pharmacokinetics of TCP and its potential prodrug CE-TCP in the rat central nervous system (CNS) after intraperitoneal administration by measuring the brain levels of CE-TCP and the TCP formed from it and comparing these to the data obtained after an equimolar dose of TCP. The effects of CE-TCP on inhibition of monoamine oxidase (MAO) and on brain levels of the neurotransmitter amines noradrenaline (NA) and dopamine (DA) relative to TCP have also been studied.

MATERIALS AND METHODS

Chemicals

The sources of drugs and chemicals used in this study were as follows: pentafluorobenzoyl chloride (PFBC), Aldrich Chemical Co. (Milwaukee, Wis.); tranylcypromine (TCP) HCl, Sigma Chemical Co. (St. Louis, Mo.); and trichloroacetic anhydride (TCAA), Pfaltz and Bauer Inc. (Stamford, Conn.). ^{14}C-Labeled β-phenylethylamine (PEA) and 5-hydroxytryptamine (5-HT) were obtained from New England Nuclear (Lachine, Québec).

N-(2-Cyanoethyl)tranylcypromine (CE-TCP) oxalate was synthesized in our laboratories by Drs. T. W. Hall and R. G. Micetich. The primary parent amine (TCP) was dissolved in benzene and refluxed with 4.7 equiv of acrylonitrile for 24 hr under an atmosphere of nitrogen. The mixture was cooled to room temperature, and the solvent and excess acrylonitrile were removed under reduced pressure (using an aspirator), to give the crude product. The pale yellow oil was purified by distillation under reduced pressure (0.1 mm Hg), which resulted in recovery of the desired *N*-cyanoethyl analogue, obtained as a colorless oil. The distilled *N*-cyanoethyl analogue was dissolved in ether and added dropwise

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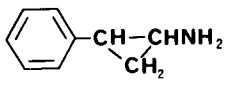
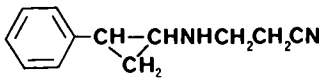


TCP



CE-TCP

Fig. 1. Chemical structures of tranylcypromine (TCP) and *N*-(2-cyanoethyl)tranylcypromine (CE-TCP).

to 1.25 equiv of oxalic acid dihydrate dissolved in a mixture of ether and methanol (6.6:1). The gelatin-white precipitate was then collected by suction filtration to give an oxalate salt of the *N*-cyanoethyl analogue. The oxalate salt of CE-TCP gave a characteristic mass spectrum, nuclear magnetic resonance spectrum (NMR), and infrared (IR) spectrum consistent with its proposed structure. NMR (free base; $CDCl_3$; 60 MHz): 1.02 (m, 2H, $CH_2<$, cyclopropyl ring), 1.88 (m, 2H, one proton exchangable with D_2O, N*H* and PhC*H*<), 2.30 (m, 1H, NC*H*<), 2.47 (t, 2H, NCH_2CH_2CN), 3.00 (t, 2H, NCH_2CH_2CN), 7.33 (m, 5H, Ph). IR (free base; neat): 3340 cm^{-1} (broad, NH), 2260 cm^{-1} (CN), 1610 cm^{-1} (C=C), 700 cm^{-1} (Ph). As further confirmation of structure, the pentafluorobenzoyl derivative of CE-TCP was prepared and subjected to electron-impact mass spectrometry. The molecular ion (*m/z* 380) and other fragment ions obtained were consistent with the structure of pentafluorobenzoylated CE-TCP. Two other important confirmatory fragment ions were *m/z* 185 (PhC_3H_3 = $\overset{+}{N}HCH_2CH_2CN$; 16.7% relative abundance) and *m/z* 81 (CH ≡ $\overset{+}{N}CH_2CH_2CN$; 45.1%). The melting point of CE-TCP was determined to be 157–158°C (dec). All reagents used were of analytical grade.

Subjects

Male Sprague–Dawley rats weighing 220–250 g were used for all experiments. The animals were kept in a temperature-controlled room (21 ± 1°C) and housed in plastic cages on cedar-chip bedding. Food and water were provided *ad libitum* and controlled conditions of a 12 hr-on/12 hr-off lighting schedule were used. The drugs CE-TCP and TCP were dissolved in physiological saline prior to administration. All animals were administered 0.1 mmol/kg of CE-TCP or TCP.

Tissue Collection and Storage

Animals were killed at specified time intervals after a single intraperitoneal (ip) injection and brains were rapidly dissected out. The meninges and pineal gland were removed and the brain tissue was immediately frozen in isopentane on solid carbon dioxide. These tissue samples were stored at −50°C until the time of analysis, at which time the brains were divided sagitally into two halves, one-half for analysis of catecholamines and drugs and the other half for measurement of MAO activity. Samples for amine and drug analysis were homogenized in 5 vol of ice-cold 0.1 *N* perchloric acid containing 10 mg% EDTA. After centrifugation at 12,000*g* for 15 min to remove protein, the supernatant was retained for analysis; 2 ml was required for analysis of drugs and 200 μl was used for analysis of catecholamines, as described below. The other halves of the brain were homogenized in isotonic KCl solution and assayed for MAO-A and MAO-B activity (using ^{14}C-5-HT and ^{14}C-PEA as substrates, respectively) using the procedure of Wurtman and Axelrod (13).

Analysis of CE-TCP and TCP

Analysis of CE-TCP was performed with a gas chromatograph equipped with an electron capture detector (GC-ECD) after derivatization with PFBC under aqueous conditions (14). Analysis of TCP was also conducted by GC-ECD, after derivatization with TCAA under aqueous conditions (15). The coefficient of variation for 100-ng samples of CE-TCP and TCP was 6.7 and 1.6%, respectively. Structures of the final derivatives were confirmed using combined GC–mass spectrometry (GC-MS). Standard curves were prepared by adding known varying amounts of CE-TCP or TCP standards and a fixed concentration (the same as that added to the brain extracts) of internal standard (*p*-chlorophenylethylamine, 200 ng) to a series of tubes. These tubes were carried in parallel through the assay procedure. The quantitation of CE-TCP and TCP in the brain extracts was based on peak height ratios of CE-TCP or TCP to that of an internal standard of fixed concentration. These ratios were compared to values obtained with the standard curves prepared for each assay run. Correlation coefficients greater than 0.99 were obtained routinely.

Analysis of DA and NA

Brain concentrations of DA and NA were determined using a Waters high-performance liquid chromatography (HPLC) apparatus with an electrochemical detector. A modification of the procedure of Kim *et al.* (16) was used. The aqueous mobile phase (1000 ml) contained 10 mmol dibasic sodium phosphate, 0.5 mmol ethylenediaminetetraacetic acid, and 5 mmol sodium octylsulfate as the ion-pairing reagent. The pH of this solution was adjusted to 2.5 with phosphoric acid. This solution was then filtered through a Millipore 0.45-μm filter membrane (filter type HA) prior to the addition of HPLC-grade 5% methanol (50 ml) and 10% acetonitrile (100 ml). The mobile phase was degassed with helium and pumped at 0.7 ml/min onto an Altex Ultrasphere-ODS analytical column (5 μ, 46-mm i.d. × 15 cm). Chromatographic separations were performed at ambient temperatures. The average coefficients of variation for all the compounds were less than 10.1% at 10 ng/ml and the correlation coefficients were greater than 0.99.

Statistical Analyses

Student's *t* test ($\alpha = 0.05$) for independent means was employed where a comparison involved only two groups. Data were otherwise analyzed with a one-way analysis of variance followed by the Newman–Keuls multiple comparison test ($\alpha = 0.05$). The standard mean error (SE) is represented by error bars in all figures.

Determination of the Area Under the Curve (AUC) and the Half-Life ($t_{1/2}$)

The trapezoidal method was employed to calculate the area under the curve (AUC) (17). Least-squares regression was employed to fit the curve and determine the half-life ($t_{1/2}$).

RESULTS

A time–concentration profile of TCP in rat brain after intraperitoneal administration of TCP is illustrated in Fig. 2. The t_{max} (the time at which the concentration is maximum) and C_{max} (maximum or peak concentration) in the rat brain, the area under the curve for the 240-min period following TCP and CE-TCP administration (AUC_{0-240}), and the elimination half-life ($t_{1/2}$) of TCP and CE-TCP from brain are summarized in Table I.

Time–concentration profiles of CE-TCP and TCP in rat brain after ip administration of CE-TCP are illustrated in Fig. 3. The levels of TCP in brain remain higher than those of CE-TCP at all times. The brain elimination $t_{1/2}$'s (β $t_{1/2}$) of CE-TCP and TCP (determined from Fig. 3) were calculated to be 263.3 ± 37.6 and 183.9 ± 38.1 min, respectively.

Brain levels of DA and NA are shown in Figs. 4 and 5, respectively. Both CE-TCP and TCP elevated levels of DA in rat brain above control levels at all time intervals after 5 min. Brain levels of NA were decreased significantly after the administration of TCP at all time intervals except 240 min in this study. The prodrug CE-TCP also decreased levels of NA in brain at certain time intervals, but this effect was much less pronounced than with TCP.

The percentage inhibitions of MAO-A and MAO-B in rat brain after the administration of CE-TCP and TCP are illustrated in Table II.

Table I. Pharmacokinetic Parameters of Tranylcypromine (TCP) in Rat Whole Brain After Intraperitoneal (ip) Administration of 0.1 mmol/kg TCP and Pharmacokinetic Parameters of *N*-(2-Cyanoethyl)tranylcypromine (CE-TCP) and Its Parent Amine TCP in Rat Whole Brain After ip Administration of CE-TCP[a]

Parameters	TCP after TCP	TCP after CE-TCP	CE-TCP
$AUC_{0-240\ min}$ (μmol min/g)	15.8 ± 0.52[a]	1.53 ± 0.09	1.17 ± 0.4
C_{max} (nmol min/g)	125.3 ± 11.5	15.0 ± 1.3	13.9 ± 1.5
t_{max} (min)	30	60	60
$t_{1/2}$ (min)	96.1 ± 11.9	183.9 ± 38.1	263.3 ± 37.6

[a] Results are means (± SE) of six experiments.

DISCUSSION

The dose used in this investigation was chosen because it is well within the range of doses of TCP frequently used to inhibit MAO in laboratory animals and is known to inhibit MAO in rat brain by greater than 80%, a level of inhibition that has been reported to result in a favorable antidepressant response to MAO inhibitors in the clinical situation (18). To make comparisons between the two drugs meaningful, an equimolar dose of CE-TCP was employed. *N*-(2-Cyanoethyl)tranylcypromine was metabolized to TCP, and readily measurable concentrations of CE-TCP and TCP were detected in the brain. The concentrations of TCP in the CNS after ip administration of CE-TCP remained higher than those of CE-TCP, and the AUC_{0-240} of TCP was higher than that of CE-TCP ($P < 0.005$, Student's t test) (Table I). The C_{max} of TCP in the rat CNS after the administration of TCP was 8.35 times larger than the C_{max} of TCP obtained after an equimolar dose of CE-TCP, but the elimination (β) $t_{1/2}$ of TCP in the CNS after the administration of CE-TCP was about 1.9 times longer than the elimination (β) $t_{1/2}$ calculated after an equimolar dose of TCP. These observations in rat brain indicate that CE-TCP may be a useful prodrug of

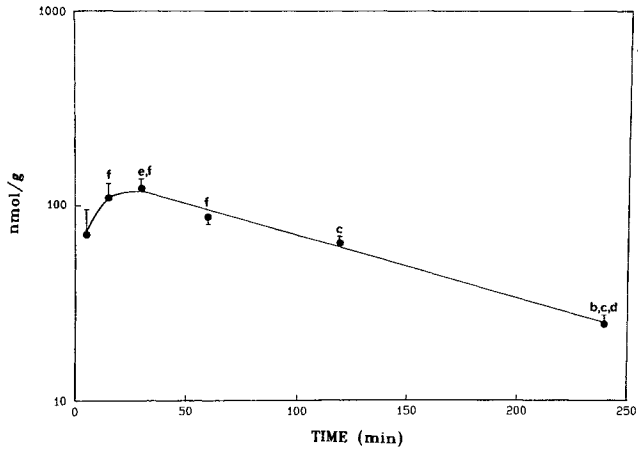


Fig. 2. A semilog plot of the levels of tranylcypromine (TCP) in rat brain after the administration of TCP (0.1 mmol/kg ip). $N = 6$. Error bars = SE. Comparisons were made with the Newman–Keuls test ($\alpha = 0.05$) following analysis of variance. Superscripts: b, different from 15 min; c, different from 30 min; d, different from 60 min; e, different from 120 min; f, different from 240 min.

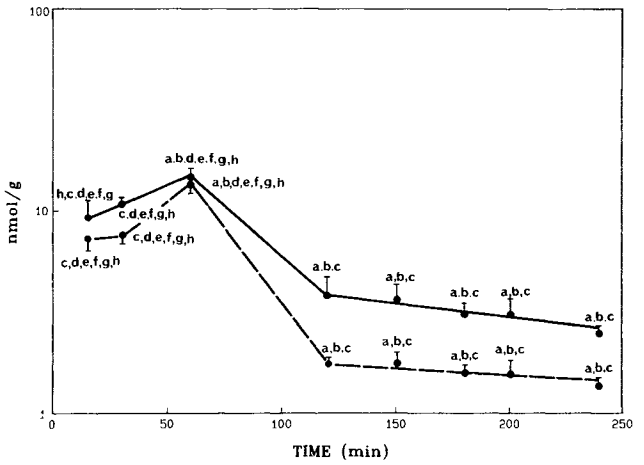


Fig. 3. A semilog plot of the levels of *N*-(2-cyanoethyl)tranylcypromine (CE-TCP; ●- -●) and tranylcypromine (TCP; ●——●) formed from CE-TCP in rat brain after the administration of CE-TCP (0.1 mmol/kg ip). $N = 6$. Error bars = SE. Comparisons were made with the Newman–Keuls test ($\alpha = 0.05$) following analysis of variance. Superscripts: a, different from 15 min; b, different from 30 min; c, different from 60 min; d, different from 120 min; e, different from 150 min; f, different from 180 min; g, different from 200 min; h, different from 240 min.

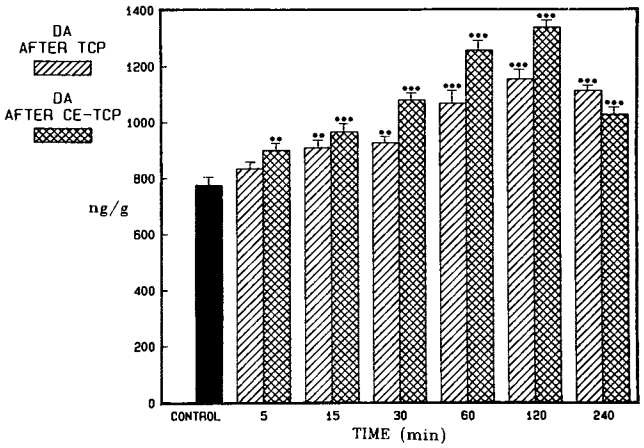


Fig. 4. Brain levels of dopamine (DA) in the rat after the administration of tranylcypromine (TCP) or *N*-(2-cyanoethyl)tranylcypromine (CE-TCP) (0.1 mmol/kg ip). $N = 6$. Error bars = SE. Significance of differences (Student's t test) from control values are indicated by (*) $P < 0.05$, (**) $P < 0.01$, and (***) $P < 0.001$. Concentrations of DA in brains of rats treated with physiological saline were not significantly different from the control values at any time interval.

TCP, resulting in lower initial brain levels of TCP than those obtained after administration of the parent drug TCP but providing a more gradual disappearance of TCP from the brain. However, it must be noted that the combined AUCs of brain levels of CE-TCP and TCP from the prodrug represent only 17% of the AUC for TCP after the administration of TCP alone. This might suggest that a larger portion of CE-TCP is distributed peripherally, resulting in higher peripheral concentrations of TCP after CE-TCP than after the administration of TCP; such a situation could have important implications, particularly with regard to hypertensive

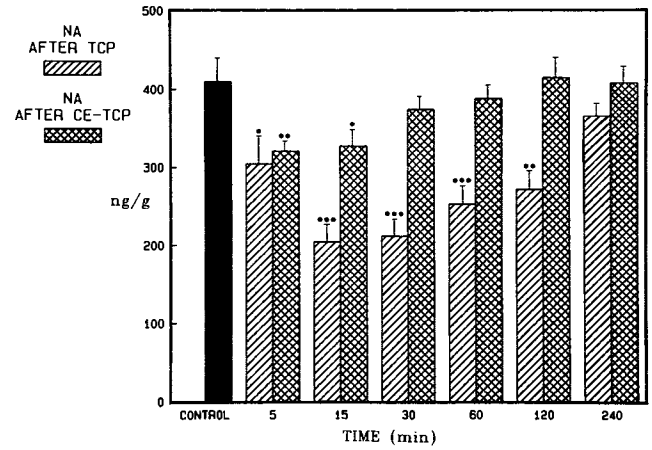


Fig. 5. Brain levels of noradrenaline (NA) in the rat after the administration of tranylcypromine (TCP) or *N*-(2-cyanoethyl)tranylcypromine (CE-TCP) (0.1 mmol/kg ip). $N = 6$. Error bars = SE. Significance of differences (Student's t test) from control values are indicated by (*) $P < 0.05$, (**) $P < 0.01$, and (***) $P < 0.001$. Concentrations of NA in brains from rats treated with physiological saline were not significantly different from control values at any time interval.

Table II. Time–Percentage Inhibition of Monoamine Oxidase Profile in Rat Brain After Administration of *N*-(2-Cyanoethyl)tranylcypromine (CE-TCP) or Tranylcypromine (TCP) (0.1 mmol/kg ip)[a]

Time (min)	% inhibition after CE-TCP treatment		% inhibition after TCP treatment	
	Of MAO-A	Of MAO-B	Of MAO-A	Of MAO-B
5	55.7 ± 4.0	70.9 ± 5.0	70.5 ± 6.8	71.0 ± 4.3
15	77.5 ± 5.6	73.4 ± 4.3	85.4 ± 4.2	89.5 ± 1.7
30	78.8 ± 5.4	75.3 ± 3.0	94.0 ± 1.1	91.2 ± 1.4
60	81.7 ± 5.4	84.2 ± 1.3	85.2 ± 4.1	90.8 ± 1.3
120	80.4 ± 3.7	83.0 ± 2.0	81.5 ± 4.3	88.0 ± 1.9
240	81.2 ± 4.9	80.5 ± 4.0	80.5 ± 3.9	84.3 ± 2.6

[a] Values represent means ± SE ($N = 6$).

side effects that may be produced by TCP. Because of this, we have conducted a preliminary study on heart levels of TCP in the rat following equimolar doses (0.1 mmol/kg ip) of CE-TCP and TCP. Results from that study indicate that in the heart, in addition to the brain, lower levels of TCP are present after the administration of CE-TCP than after TCP [$AUC_{0-240\ min}$ for TCP of 2.03 and 9.67 μmol min/g, respectively (Nazarali, Baker, Coutts, and Greenshaw, unpublished)].

Both CE-TCP and TCP caused DA levels to rise above control in a similar pattern (Fig. 4), although this increase was slightly greater with CE-TCP than with TCP at most time intervals. Brain levels of DA reached a maximum at 120 min with both drugs. At 240 min, levels of DA showed a trend toward a return to baseline after both CE-TCP and TCP, although levels still remained significantly higher than control values.

Brain NA levels were significantly depleted after the administration of TCP at all time intervals except at 240 min (Fig. 5). Similar findings of depleted NA levels in rat diencephalon after a single .12-mmol/kg ip dose of TCP have been reported by others (19,20) using 1.2 times the dose used in this study. These results may reflect the fact that TCP is known to have relatively marked effects on release and reuptake of NA at nerve terminals (21–26). At the dose used in the experiments reported here, sufficiently high brain concentrations of TCP are attained for the drug to be having these marked effects on NA. The resultant NA present in the synaptic cleft is probably inactivated by the enzyme catechol *O*-methyltransferase (COMT) (27).

Brain levels of NA after CE-TCP were depleted significantly at 5 and 15 min, with levels gradually returning to control levels at subsequent time intervals. This probably reflects the lower levels of TCP in the brains of the CE-TCP-treated rats at all time intervals studied.

Administration of the prodrug CE-TCP causes strong inhibition of both type A and type B MAO. Other studies *in vitro* in our laboratories (28) have demonstrated that CE-TCP, at a concentration of 4 μ*M* (similar to brain levels observed at 120 min in this study; see Fig. 3), is equipotent to TCP in inhibiting MAO-A and MAO-B. Mean percentage inhibition values (±SE; $N = 6$) for MAO-A and -B were, respectively, 81.7 ± 3.1 and 85.6 ± 1.2 for CE-TCP and 87.4 ± 1.6 and 94.2 ± 1.4 for TCP (28). No significant difference

(Student's t test, $P > 0.05$) was observed for MAO-A inhibition between the drugs; however, a significant difference was observed for MAO-B inhibition between TCP and CE-TCP. It is therefore likely that unmetabolized CE-TCP is also contributing to the MAO inhibition seen in the brain after the administration of CE-TCP. The percentage inhibition values *in vivo* indicate maximum inhibition occurring at 60 and 30 min after the administration of CE-TCP and TCP, respectively (Table II). Brain concentrations of CE-TCP and TCP, respectively, were highest at these times (Figs. 2 and 3).

These studies indicate that TCP is detected in the brain after the administration of CE-TCP and that extensive inhibition of MAO *in vivo* is observed. We have previously reported that CE-TCP causes elevations of brain levels of the putative neurotransmitter 5-hydroxytryptamine (5-HT; serotonin) in a pattern similar to that seen after the administration of an equimolar dose of TCP (28). The present investigation has demonstrated that CE-TCP causes effects similar to those of TCP (when both drugs are administered at a dose of 0.1 mmol/kg) on inhibition of MAO and on brain levels of DA but produces a much less pronounced decrease in NA concentrations. This last effect could have important clinical implications since TCP's actions on NA uptake and/or release have been proposed to contribute to the production of hypertensive cerebrovascular effects (25). Thus CE-TCP not only may provide more consistent brain concentrations of TCP but also may represent a means of obtaining good inhibition of MAO while decreasing the adverse side effects of TCP. Detailed dose–response studies of both drugs in brain, liver, and heart should shed further light on this aspect and on the formation of TCP from CE-TCP. The results of the present investigation on one equimolar dose for both drugs indicate that such studies are warranted.

ACKNOWLEDGMENTS

This study was supported by the Alberta Provincial Mental Health Advisory Council (PMHAC), the Medical Research Council of Canada, and the Alberta Heritage Foundation for Medical Research. Sincere thanks are due to Dr. A. J. Greenshaw for his advice and assistance with statistical procedures. Drs. R. G. Micetich and T. S. Hall are acknowledged with gratitude for the synthesis of *N*-(2-cyanoethyl)tranylcypromine. The authors are grateful to Miss H. Schmidt and Mrs. L. Hein for typing the manuscript.

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