Biochemical Pharmacology, Vol. 29, pp. 2149–2150.

0006-2952/80/0801-2149 $02.00/0

Trazodone, a new nontricyclic antidepressant without anticholinergic activity

(*Received* 12 *January* 1980; *accepted* 15 *February* 1980)

Tricyclic antidepressant therapy is associated with atropine-like side effects including difficulty in urination, exacerbation of glaucoma symptoms, dry mouth and constipation [1]. These may be hazardous to the patient or interfere with compliance by middle-aged and elderly individuals who constitute the majority of the population being treated for depression. Trazodone (Desyrel) is a new antidepressant agent which is therapeutically equivalent to the tricyclic antidepressants. It has a rapid onset of action, with beneficial therapeutic effects evident by 3–7 days [2]. The pharmacological profile of trazodone is quite different from that of the tricyclic antidepressants and reveals a low level of anticholinergic activity in standard tests with laboratory animals [3]. We have obtained *in vitro* biochemical evidence, corroborated by *in vivo* test data, which predicts that trazodone therapy will exhibit a lower incidence of anticholinergic side effects compared to the conventionally used tricyclic compounds.

The displacement of [^{3}H]-3-quinuclidinyl benzilate ([^{3}H]QNB) from washed membranes [4] obtained from rat hippocampi was used to evaluate the relative affinities of trazodone and various tricyclic antidepressants for muscarinic cholinergic binding sites. Male Sprague–Dawley rats were decapitated, the brains removed, and the hippocampi dissected and held at −80° until required. Pooled hippocampi were homogenized (Polytron), and membranes were recovered and washed once by centrifugation at 39,000 *g* for 10 min in 200 vol. of HEPES-KOH, pH 7.4.* The washed membranes were resuspended in 20 vol. of ice-cold buffer. Specific binding was measured by incubating membranes (75–100 μg protein) in the presence of 33 pM [^{3}H]QNB (New England Nuclear, sp. act. = 29.4 Ci/mmole; less than K_D of 75 pM) and drug in duplicate for 90 min at 25°. Atropine (10 μM) displaced 87 per cent of the total counts bound. Filtration and counting techniques have been described [4]. The IC_{50} values were obtained from linear regression analysis of log-probit plots at five concentrations of each drug.

The *in vivo* estimate of anticholinergic activity was obtained in fasted, male Charles River (CD-1) mice. Various dose levels of drug were administered orally and, at a previously determined time of peak effect, the animals were injected with 1.25 mg/kg, i.p., physostigmine sulfate ($> LD_{99}$). Drugs were tested at three or more dose levels on groups of ten mice. Animals observed alive after 1 hr indicated positive anticholinergic activity. The ED_{50} values (and 95 per cent fiducial limits) were determined according to the method of Berkson [5].

The results of these experiments are shown in Table 1. The tricyclic antidepressants have 0.1–0.5 per cent the potency of atropine in inhibiting the binding of [^{3}H]QNB *in vitro*, while trazodone is 150- to 800-fold weaker (0.0007 per cent of atropine). Trazodone was not found to possess anticholinergic activity *in vivo* whereas all of the tricyclic compounds demonstrated atropine-like activity.

A dose of trazodone comparable to that clinically administered to humans [2] would yield an equilibrium plasma concentration of 200–600 nM in rats [6]. The therapeutic steady-state concentration of imipramine has been determined to be 450–800 nM, and plasma levels for other tricyclic compounds are in the same range [7]. Thus, the *in vivo* plasma concentrations of trazodone and the conventional tricyclic antidepressants which result in therapeutic benefit are probably spread over the same concentration range. In particular, the therapeutic plasma concentrations of the tricyclic antidepressants are of the same order as the concentrations found to inhibit cholinergic binding by 50 per cent *in vitro*, while the predicted therapeutic plasma concentration of trazodone is less than 0.8 per cent of the IC_{50} *in vitro*. Therefore, it would be predicted that a therapeutically equipotent regimen of trazodone, compared to conventional tricyclic antidepressant therapy, would lack the anticholinergic side effects associated with the latter. In fact, a recent 15-center double-blind trial revealed a significantly higher incidence of anticholinergic side effects for imipramine versus trazodone or placebo, while there was no significant difference in side effects when trazodone and placebo were compared [8]. In addition to the important clinical implications of our work, there is the suggestion that, in contrast to current thinking (see Ref. 9 for a brief review), cholinergic mechanisms may have little influence on the pathophysiology and pharmacotherapy of affective illness.

In summary, the anticholinergic activity of trazodone, a new non tricyclic antidepressant, was compared with other established tricyclic antidepressants. [^{3}H]QNB binding was used as the *in vitro* method for comparing anticholinergic activity. Prevention of death after physostigmine administration was used as the *in vivo* estimate of activity. Trazodone was found to have much less anticholinergic activity than the tricyclic antidepressants.

Acknowledgements—We are grateful to Mr. Lloyd E. Allen and Mr. Donald E. Thomas for their technical assistance and to Mrs. Laura Warner for help in preparing the manuscript.

* Abbreviations used: HEPES, 4-(2-hydroxyethyl)-1-piperazine-ethanesulphonic acid; and IC_{50}, concentration required to produce 50 per cent inhibition.

Table 1. *In vitro* and *in vivo* estimates of anticholinergic activity of antidepressants*

Drug	Inhibition of [^{3}H]QNB binding, IC_{50} (nM)	Inhibition of physostigmine lethality, ED_{50} (μmoles/kg)
Atropine	0.51 ± 0.41	4.0 (2.9–5.6)†
Trazodone	75,300 ± 500‡	> 980§
Amitriptyline	160 ± 90	58 (47–71)
Comipramine	170 ± 40	537 (340–770)
Desipramine	470 ± 170	538 (390–730)
Imipramine	94 ± 38	230 (190–280)

* Each result is the mean ± S.E.M. for three different hippocampal preparations.

† Ninety-five per cent fiducial limits in parentheses.

‡ $P < 0.01$ vs all other compounds (paired Student's *t*-test).

§ No protection provided at this dose.

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