Quipazine, a New Type of Antidepressant Agent*

RODOLFO RODRÍGUEZ and EFRAÍN G. PARDO
Instituto Miles de Terapéutica Experimental, México, D.F. México

Received October 26, 1970
Final Version: January 25, 1971

Abstract. Quipazine, (2-(1-piperazinyl)quinoline), is comparable to the tricyclic antidepressants in many of its pharmacological effects. Common properties include the ability to antagonize reserpine and tetrabenazine sedation in mice and rats, to reverse reserpine hypothermia in rats and to inhibit selectively the mouse-killing behavior of rats. In all these actions, quipazine is approximately equipotent with imipramine, desipramine and amitriptyline. Quipazine is far less effective than imipramine in potentiating the locomotor stimulation elicited by d-amphetamine. Quipazine differs from tricyclic antidepressants in that it does not enhance responses induced by exogenous or endogenous norepinephrine and does not block the effects of indirectly acting sympathomimetic amines. Furthermore, quipazine, unlike imipramine, counteracts tetrabenazine induced sedation in catecholamine depleted animals. These findings suggest that the pharmacological actions of quipazine do not involve adrenergic mechanisms.

Key-Words: Quipazine — Antidepressants — Serotonin.

Since the discovery of the clinical antidepressant activity of imipramine by Kuhn in 1957, a widespread search has been made for new and structurally different types of compounds which might have a similar therapeutic effect in depressed patients. Most of the new drugs that have been tested and proven effective in man as antidepressant agents are dibenzazepine derivatives. None of the known compounds possesses significant advantages over imipramine (Davis, Klerman and Schildkrut, 1968).

Screening studies on a large group of piperazine derivatives revealed that one of these, 2-(1-piperazinyl)quinoline, (which will henceforth be referred to as quipazine, its generic name), a compound previously reported to possess significant smooth muscle stimulating properties (Hong and Pardo, 1966), counteracted the ptotic and sedative effects of reserpine in mice. Since this effect is an indicator of potential antidepressant ability, and in view of the interesting pharmacological analogy between quipazine and serotonin (Hong, Sancilio, Vargas and Pardo, 1969), it was

* A preliminary report of this work was presented at the II International Seminar on Psychophysiology and Psychopharmacology, Mexico City, Dec. 3, 1969.
decided to confirm and further evaluate the psychopharmacological properties of quipazine. Results of such studies constitute the basis of the present communication. Quipazine has the following chemical structure:

\[
\begin{align*}
\text{N} & \quad \text{CH-COOH} \\
\text{N-H} & \quad \text{II} \\
\text{CH-COOH} & \\
\end{align*}
\]

2-(1-PIPERAZINYL)QUINOLINE MALEATE

Materials and Methods

Acute Toxicity

The acute intraperitoneal and oral toxicities were determined in male CFW mice weighing 18 to 25 g and in male Wistar rats weighing 150 to 250 g. LD\textsubscript{50}s and 95\% confidence limits were calculated by the method of Litchfield and Wilcoxon (1949), based on deaths occurring up to 72 h following administration.

Blockade of Mouse-Killing Behavior

The influence of compounds on the mouse-killing behavior of rats was determined with a slightly modified version of the test described by Horovitz, Piala, High, Burke and Leaf (1966). Male Wistar rats weighing between 130 and 280 g were used in this study. Animals were selected from the rat colony that would spontaneously attack and kill a mouse within 15 sec after confrontation. These animals were repeatedly confronted with mice in order to insure prompt and consistent attack. Each rat was tested for mouse-killing behavior prior to drug treatment and at 15, 30 and 60 min after intraperitoneal administration of the drug. Ten rats were used at each dose level. ED\textsubscript{50}s were calculated by the method of Litchfield and Wilcoxon (1949) at the time when maximal effect of each drug was observed. Because a blockade of the mouse-killing behavior might have been simply a manifestation of ataxia, the effect of the same compounds on coordinated motor activity was evaluated in normal Wistar rats using the rotarod apparatus (Dunhan and Miya, 1957). In this study, rats were trained to walk for at least 2 min on a wooden rod, 2 inches in diameter, rotating at 13 rpm. After drug treatment, animals were placed on the rotarod at the same time intervals indicated above. Rats unable to remain on the rotarod for 100 sec were scored as effected. Mean neurotoxic doses were calculated at the time of maximal inhibition of mouse-killing response.