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THE NEUROCHEMICAL PROFILE OF LONG TERM ORAL ADMINISTRATION OF MOCLOBEMIDE

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ABSTRACT

Moelobemide, a heir amide derivative. predominantly inhibits the A D. of monoamine oxidase (MAO) and its MAO binding is reversible. Acute administration of moclobemide been shown to induce in brain levels of monoamines and a concomitant decrease in their respective metabolite. In the present study, the drug was administered to rats *oral*ly in drinking water at doses of 0.5-1.0 mg/day/rat of an average weight of 250g for three weeks. This was equivalent to the recommended human dose of 150-300 mg/day. The drug administrant, did not alter food intake growth rate and activity of rats. Drain levels of 5-hydmnanplatnine (3-ihI) and dopamine (DA) increased. However, increases in 5-hydroxylndoleacetic acid (5-HIAA), dihydroxvphenylacetic acid (DOPAC) and horn Millie acid (HVA) ac reported in acute studies were not observed following chronic drug administration in the present study. In addition an increase in Main levels of tryptophan also occupied. Neurochemical profile of long term moclobemide administration is explainable in terms of an inhibition of MAO activity, increased availability of 5-HT precursor tryptophan, and decreased egress of monoamine metabolites.

INTRODUCTION

The enzyme which metabolizes biogenic amines by oxidative deamination MAO (Monoamine-oxvgenoxidoreductase-deaminating, flavin containing. EC 1.4.3.4.; Zeller, 1938) exist in two catalytically distinguishable forms termed as MAO-A and MAO-B. MAO-A prefers 5-hydroxytryptamine (5-HT), noradrenaline (NE) and adrenaline (E) as substrates and is selectively inhibited by clorgyline. MAO-B preferentially deaminates phenylethylamine and benzylamine. 1-deprenvl being a relatively specific inhibitor. Tyramine and dopamine (DA), however, are good substrates for both enzyme forms (Johnston, 1968: Yang and Neff. 1974; Fowler and Callingham, 1978 Suzuki et al., 1982).

Since their introduction into the therapy in the 1950s, the irreversible MAOIs have been a mainstay in the therapy of affective disorders. However, these irreversible MAOIs of the first generation have been discredited by reports perpetuating the belief that MAO inhibition could produce severe liver toxicity (Dostert, 1984) and pronounced orthostatic hypotension (Goldman et al., 1986). The negative attitude against MAOIs also originated from reports on the so called "cheese reaction," the marked enhancement of the pressor effect of tyramine present in nutrients and specially in fermented cheese (see Haleem, 1994). It should be stressed that, fatal hypertensive

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crisis was observed only with irreversible and non selective MAOIs of the first generation when patients ingested excessive quantities of foods and beverages with a high tyramine content.

Moclobemide, a benzamide derivative, predominantly inhibits the A form of MAO and is characterized by the fact that its MAO binding is reversible (Burkard et al., 1989; Da Prada et al., 1989). Pharmacological studies have suggested that compared with irreversible MAOI such as tranyypromine (Berlin et al., 1989), moclobemde is a safe drug with respect to potentiation of action of tyramine. Moclobemide has been used safely in therapeutic trials without dietary tyramine restrictions. Double blind comparative clinical trials have shown that the efficiacy of moclobemide was superior to placebo (Casacchia et al., 1984) and many tricyclic compounds such as clomipramine (Larsen et al., 1984). amitryptyline (Norman et al., 1985), desipramine (Stefanis et al., 1984) and imipramine (Baumhackl et al., 1989; Versiani et al., 1989). Moclobemide was tolerated better than tricyclics with regard to anticholinergic symptoms and cardiovascular effects.

It has been shown in neurochemical investigations that acute administration of moclobe-. mide induces an increase in rat brain levels of 5-HT, DA and NA and a concomitant decrease of their deaminated metabolites 5-hydroxyindoleacetic acid (5-HIAA), dihydroxyphenyl acetic acid (DOPAC), homovanillic acid (HVA) and 3-methoxy 4-hydroxy phenyl glycol (MHPG). In the present study we report neurochemical effects of long term administration of moclobemide in rats. The drug was administered orally in drinking water at doses that equivalent to the recommended human doses of 150-300 mg/day.

MATERIALS AND METHODS

Male albino Wistar rats weighing 240-260g purchased from AK Medical University were housed individually under a 12:12h light: dark cycle (lights on at 6:00h) and controlled room temperature (22±2°C) with access to cubes of standard Indent diet for at least 3 days before experimentation.

Experimental protocol:

Animals were randomly assigned as controls and test groups. Moclobemide (ROCHE 150) was administered orally in drinking water at doses that corresponded to doses recommended for humans i.e. 150-300mg/day/70kg body weight. Average daily intake calculated for rats of average weight 250g was 0.5-1.0 mg/day. The drug was administered for three weeks in drinking water at concentration of 1 mg/100 ml of water during the first week and 2 mg/100 ml of water during the 2nd and 3rd week. Daily intake of drug was calculated by the volume of water consumed/day. Intake of drug was 0.5 ± 094 mg/day during the first week and 1.0 ± 0.15 mg/day during the 2nd and 3rd week. Food was available for 24 h to both the groups of rats. Food intakes and body weight changes were monitored weekly. No significant effect of drug administration was observed on weekly changes of food intakes and growth rates (data not shown). After three weeks of drug administration both the groups of rats were decapitated and brain samples stored at -70°C for the determination of tryptophan, 5-HT, 5-HIAA, DA, DOPAC and HVA by HPLC-EC as described by Haleem and Haider (19%). Plasma samples were also collected and stored for the determination of tryptophan by HPLC-EC (Haleem and Haider, 1996).

Statis*t*ical *analysis:*

Data were analyzed by student's t-test. P values > 0.05 were considered insignificant.

RESULTS AND DISCUSSION

Fig. 1 shows that oral administration of moclobemide for three weeks increased brain levels of tryptophan ($p < 0.001$), 5-HT ($p < 0.001$) and DA ($p < 0.001$). Mean values of 5-HIAA, DOPAC and HVA were smaller in moclobemide treated than water treated rats. Differences by t-test were insignificant.

MAOIs were the first specifically effective dregs used in the treatment of mood disorders (Ban, 1969; Pare, 1985; Dawson, 1987). They were however discredited rapidly and neglected for fear of potentially fatal effects i.e. acute hepatotoxicity and sudden hypertensive crisis. The present study shows that moclobemide administration in drinking water at doses 0.5-1.0 mg/day for three weeks to rats produced no fatal effects. Food intakes, body weights and exploratory activities of drug administered and water administered rats were highly comparable (data not shown).

The present results show that long term administration of moclobemide increased brain 5-HT and DA concentration without producing a significant decrease in their metabolites 5-HIAA, DOPAC and HVA. In vitro experiments support the concept that moclobemide is a specific compound that does not inhibit enzymatic system other than MAO. It did not modify the activity of enzymes involved in the synthesis of monoamines. Thus the activity of tyrosine hydroxylase, dopa decarboxylase, DAB-hydroxylase and phenylethanol amino N-methyl transferase was not altered by moclobemide (Keller et al., 1978; 1987). Moclobemide ex vivo produced no effect on the synaptosomal uptake of monoarnines and did not induce NA release from the brain slices (Keller et al, 1978). Moclobemide did not induce turning behaviour in rats lesioned unilaterally by the injection of 6-hydroxydopamine (6-OH-DA) into the median forebrain bundle (Da Prada et a1., 1981). Binding experiments show that moclobemide is without effect at serotonergic, adrenergic, cholinergic and histaminergic binding sites (Da Prada et al., 1989). An increase in monoamine (5-HT and DA) concentration in the absence of significant decrease in the concentration of their metabolites (5-HIAA, DPAC and HVA) as observed in the present study is, therefore, explainable in terms of decreased degrees of monoamine metabolites. Increase of brain tryptophan could also, at lease partially, contribute in the enhancement of brain 5-HT concentration. Ttyptoplmn hydroxylase, the rate limiting enzyme of 5-HT biosynthesis, exists unsaturated with its. Therefore, factors which increase brain tryptophan concentration also increase 5-HT synthesis (Haleem, 1990; Haleem et al., 1998).

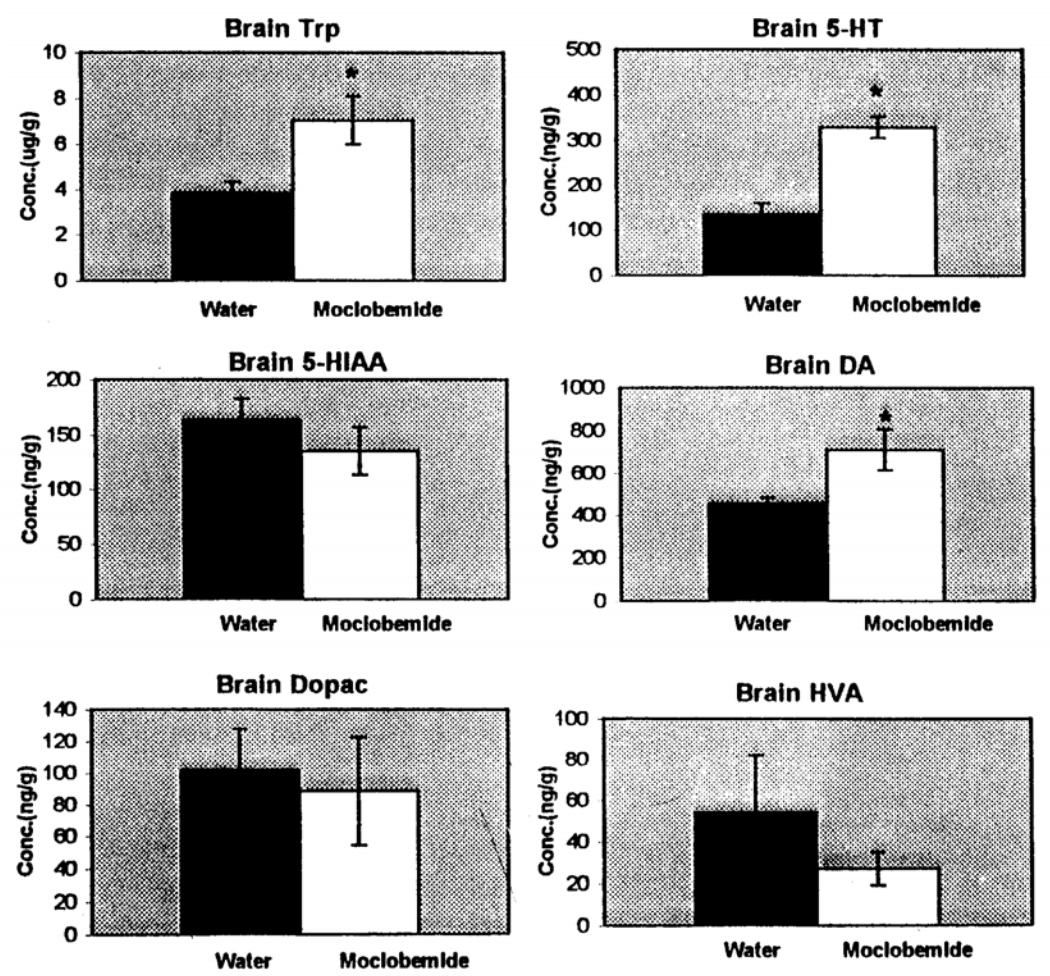

Fig. l: Effects of 3 weeks moclobemide administration on brain levels of Try ptophan (ug/g), 5-HT, 5-HIAA, DA, DOPAC and HVA (ng/g). Values are means ± SD (n=6). Significant differences by student t-test. *$p < 0.001$.

In conclusion, the present study shows that administration of moclobemide orally in drinking water to rats for a period of three weeks at doses of 0.540 mg/day/250g rat (calculated from doses recommended for human i.e. 150-300 mg/day) produced no adverse effect. Increases of brain 5-HT and DA concentration following this long term administration could occur due to an inhibition of the activity of degradation enzyme MAO-A. Like other antidepressants moclobemide is also thought to act by potentiating monoamine functions in the brain. The neurochemical profile of

long term administration of moclobemide as observed in the present study suggests that the drug could potentiate monoamine functions by inhibiting their degradation Enhanced availability of tryptophan could also be at least partially involved in the observed enhancement of brain 5-HT. Lack of moclobemide's effect on monoamine metabolites is explainable in terms of their decreased egress.

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