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Effects of Tiapride on Homovanillic Acid Levels in Human Cerebrospinal Fluid Drawn at Pneumoencephalography

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Abstract. The effect of tiapride on HVA and 5-HIAA levels in the CSF drawn at pneumoencephalography (PEG) was studied. Five consecutive 5 ml fractions of CSF were drawn from control and tiapride-treated subjects. In both groups, a linear increase in HVA concentrations was found between the first and subsequent fractions. On the contrary, no significant difference in 5-HIAA concentrations was found in sequential CSF samples. Tiapride increased the mean HVA concentrations and caused a steeper caudocranial gradient of this metabolite but failed to modify 5-HIAA concentrations. The results suggest that tiapride blocks dopamine (DA) receptors and increases DA synthesis.

Key words: Tiapride – Homovanillic – 5-HIAA – Cerebrospinal fluid – Pneumoencephalography

Tiapride (N-(diethyl-aminoethyl)-methosy-5-sulphonyl-benzamide) is a novel benzamide derivative used for the relief of anxiety and aggressiveness in the elderly (Choussat 1977), in the treatment of different behavioural and neurological disturbances in alcohol adicts (Robillard 1975) and as an analgesic (Sambin 1977). Finally, tiapride seems to be useful in reducing abnormal involuntary movements such as tics, tremors and L-DOPA induced dyskinesias (Emile et al. 1977; Lhermitte et al. 1977; Pasquier and Pouplard 1977; Trillet et al. 1977).

As yet, the mechanism of action of this compound is unclear. Animal experiments have shown that, similarly to typical neuroleptics and other benzamide derivatives, tiapride increases brain dopamine (DA) turnover and activates tyrosine hydroxylase activity (Tissari et al. 1979) but is weak in displacing ^{3}H-DA and ^{3}H-haloperidol from specific binding to DA receptors (Jenner et al. 1978). Moreover, tiapride differs from typical neuroleptics in that it fails to block DA-sensitive adenylate cyclase in striatal homogenates (Portaleone et al. 1977: Elliot et al. 1977; Spano et al. 1979). To explain the different neurochemical profiles of tiapride and other benzamide derivatives on one hand, and typical neuroleptics on the other, the existence of two kinds of DA receptors in the brain has been suggested: one linked to and the other independent of adenylate cyclase (Kebabian 1978; Spano et al. 1979). The latter includes presynaptic DA receptors controlling DA synthesis and release (Di Chiara et al. 1978; Tissari et al. 1978). The aim of this study was to investigate whether tiapride in therapeutic doses affects DA and serotonin metabolism in the central nervous system (CNS) of human subjects. Changes in the concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) in the cerebro spinal fluid (CSF) were considered as an index of parallel changes in serotonin and DA metabolism in the CNS, respectively. Pneumonencephalography (PEG) was selected for this study since it can provide information on the concentrations of the acid metabolites in different CSF compartments.

Materials and Methods

A total of 11 male subjects aged between 27–61 years were chosen from 30 who had undergone diagnostic PEG for suspected adult hydrocephalus. The present study included only those patients showing a normal PEG pattern of air distribution and no signs of extrapyramidal disorders. All had been free of drugs known to affect monoamine metabolism for at least 6 weeks.

Tiapride administration was considered ethically correct to prevent vomiting and headache associated with PEG (Zenglein et al. 1978). Informed consent was obtained in all cases. Two hours after their last meal, 6 subjects received an IV infusion (500 ml in 10 h) of saline solution containing tiapride 0.4 mg/ml for a total dose of 200 mg. The remaining 5 subjects received the corresponding volume of saline. At 8 a.m., at the termination of infusion and after 12 h of

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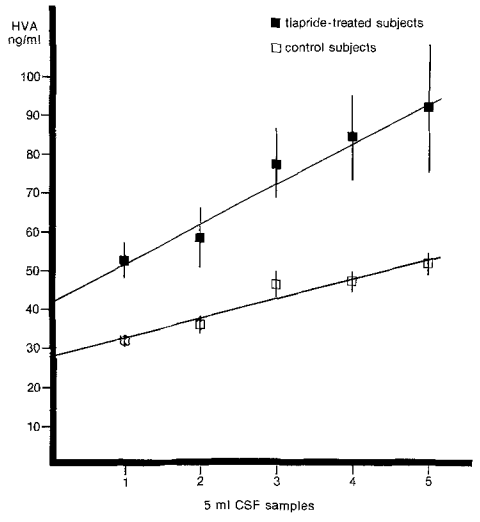

Fig. 1. HVA concentrations in five serial CSF fractions withdrawn at PEG. Each point is the mean ± S.E. of 6 tiapride-treated and 5 control subjects. Mean individual concentrations, calculated per total amount of fluid drawn, were 71.7 ± 4.7 and 42.9 ± 1.8 ng/ml in the tiapride-treated and control subjects, respectively ($P < 0.001$)

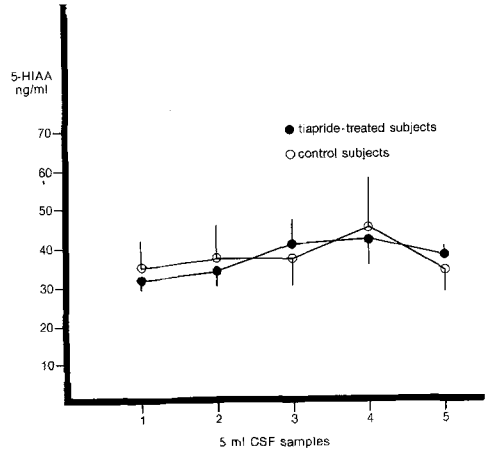

Fig. 2. 5-HIAA concentrations in five serial CSF fractions. Each point is the mean ± S.E. of 6 tiapride-treated and 5 control subjects. Mean individual 5-HIAA concentrations were 36.8 ± 1.9 and 37.5 ± 1.9 ng/ml in tiapride-treated and control subjects, respectively

fasting, PEG was carried out with the subject in the sitting position. Before intrathecal introduction of air, two 5 ml samples of CSF were withdrawn, the first for routine cytochemical analysis and the second for the present study. Immediately afterwards, 7 ml of air were slowly injected and a third 5 ml sample of CSF was removed. This procedure was repeated 4 times till a total of 30 ml of CSF had been collected. HVA was extracted as described by Biggio and Piccardi (1973) and measured fluorimetrically by the method of Andèn et al. (1963). 5-HIAA was determined according to Biggio et al. (1972). Methods of statistical evaluation were carried out as reported in the results.

Results

The mean individual HVA concentrations in the CSF calculated per total amount of fluid withdrawn (25 ml) were significantly higher in tiapride-treated subjects than in controls (Fig. 1). In both control and tiapride-treated subjects, there was a linear increase in HVA concentrations between the first and last fraction of CSF drawn. Thus, HVA concentrations were correlated ($r^2 = 0.963$ and $r^2 = 0.931$ for tiapride-treated and control subjects respectively) with a linear equation to the order in which the fractions were drawn and a reliable estimate of the caudo-cranial concentration gradient for HVA could be made from the least square straight line. The slope of this line was significantly steeper ($P < 0.01$) in the tiapride-treated group than in controls.

In contrast to the HVA results, tiapride did not influence 5-HIAA levels. Moreover, 5-HIAA levels were poorly correlated with the order of sampling (Fig. 2); the intra-individual differences in 5-HIAA concentrations between the first and each subsequent sample, treated with a paired Student's t-test, were not significant in either group.

Discussion

Little has been reported on the use of CSF drawn at PEG in the study of central monoamine metabolism (Eccleston et al. 1970; Moir et al. 1970; Garelis and Sourkes 1973, 1975). The technique of Spissu et al. (1976), used in this study, permits the removal of large amounts of CSF allowing the comparison of HVA and 5-HIAA levels in the same serial fraction. This may provide information on the rate of production and possibly the site of origin in the CNS of these monoamine metabolites. In fact, HVA levels decrease from the ventricular to the cisternal to the lumbar CSF compartments (Moir et al. 1970; Garelis and Sourkes 1973; Sjöström et al. 1975). This gradient is due to a balance between the rate of HVA production in the caudate nucleus from which most of the CSF HVA is derived (Curzon et al. 1971; Garelis and Sourkes 1973) and the rate of active transport of this metabolite from the CSF during its flow to the lumbar region. The linear HVA increase from fractions 1 to 5, measured by the slope, reflects this caudo-cranial concentration gradient. On the other hand, the lack of significant differences in 5-HIAA levels between the first and subsequent CSF samples arises from the fact that most of the serotonin metabolite derives from the spinal cord (Curzon et al. 1971; Bulat and Zivcovic 1971; Post et al. 1973; Garelis and Sourkes 1973, 1974; Weir et al. 1973). Since tiapride did not influence CSF 5-HIAA concentrations and assuming that the active transport mechanism is the same for 5-HIAA and HVA, the possibility that HVA increase is due to inhibition of the transport can be excluded Therefore, our data indicate that tiapride increases HVA production secondary to

an increased turnover of striatal DA, in agreement with results of animal experiments (Tissari et al. 1979). Accordingly, our results suggest that clinical doses of tiapride block DA receptors in humans. However, the problem arises as to the nature of these receptors. Recent experiments in our laboratory indicate that neuroleptics still increase DA synthesis in the striatum even after destruction of postsynaptic DA receptors with kainic acid, suggesting that the DA receptors, blockade of which results in stimulation of DA synthesis, are presynaptic and not, as generally considered, postsynaptic (DiChiara et al. 1978). Therefore, the tiapride effect on HVA does not necessarily reflect a blockade of postsynaptic DA receptors and dopaminergic transmission. On the contrary, this effect may reflect an increased DA release and activity. This conclusion may apply to other neuroleptics as well. More information, especially from chronic treatment, is needed to correlate the effect of tiapride on DA metabolism with its anti-psychotic and analgesic effects and its therapeutic efficacy in hyperkinetic-dyskinetic syndromes.

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