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Cerebrospinal Fluid Levels of Chlorpromazine and Its Metabolites in Schizophrenia

S. AXELSSON[1], S. JÖNSSON[2], and L. NORDGREN[3]

[1]Histologiska institutionen, Biskopsgatan 5, S-223 62 Lund, Sweden
[2]Forskningslaboratoriet, St. Lars sjukhus, Fack, S-220 06 Lund 6, Sweden
[3]Psykiatriska kliniken II, St. Lars sjukhus, Fack, S-220 06 Lund 6, Sweden

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SUMMARY. The concentrations of chlorpromazine and some of its metabolites in blood plasma and CSF from chlorpromazine-treated schizophrenics with different therapeutic results were studied. Compared to a good responder a poor responder showed very high levels of the inactive metabolite chlorpromazine sulphoxide in the CSF.

KEY WORDS: Chlorpromazine - Chlorpromazine Metabolites - Cerebrospinal Fluid - Schizophrenia.

The correlation between plasma levels of neuroleptic drugs, i. a. chlorpromazine (CPZ), and their metabolites on one hand and the clinical effects on the other has been rather extensively studied by several groups. The correlations are only partial and the picture is still somewhat confusing. In our own studies (unpublished data) on the relationship between plasma level and clinical effects we made the same experience. As the cerebrospinal fluid (CSF) levels of drug and drug metabolites can be supposed to show a closer resemblance to and co-variation with the drug concentration at the brain receptors it seemed to be of interest to investigate the levels of CPZ and CPZ metabolites in this body fluid.

This preliminary study comprises three patients, one psychotic patient whose symptoms vanished during CPZ therapy ("good responder"), one psychotic patient whose symptoms were not affected by the same therapy ("poor responder") and one CPZ-free control.

CASE REPORTS

A. Good Responder - Male, 27 Years of Age

After two years successful university studies this patient became more socially withdrawn and so disturbed by his difficulties in concentration that further studies became impossible eight months before admission. Overt psychotic symptoms had been present since

about one month before admission. At examination the patient was fully lucid. He admitted thought blocking and crowding as well as auditive perceptual disturbances. He further demonstrated neologisms and crude delusions of persecution. The patient reintegrated during CPZ therapy and on the eighth day of treatment when taking 1200 mg CPZ daily lumbar puncture (LP) was performed.

B. Poor Responder - Female, 24 Years of Age

Since about seven months the patient had experienced thought disturbances - crowding, withdrawal and intrusion attributed to outside agencies - and delusions of influence. During this period she had been treated with CPZ in a maximal dosage of 1200 mg daily. When readmitted her complaints remained unchanged. CPZ was discontinued for two weeks and then resumed. After eight days of CPZ treatment at which time the patient took 1200 mg daily, LP was performed. She had then experienced only a slight diminuition of anxiety. It should be mentioned that the patient on the first day of CPZ treatment was given 100 mg of the drug intramuscularly with neither subjective nor objective effects.

C. Control - Male, 43 Years of Age

This patient was admitted to the clinic by the National Health Insurance Authorities to get a psychiatrist' s opinion on longstanding lower back pains. The patient was neither complaining of any psychic symptoms nor did he reveal any signs of insufficiency during his stay at the ward. No CPZ was given.

METHODS

Cerebrospinal fluid was obtained by LP with a fine needle technique. The CSF and plasma samples were analysed according to a modification by Christoph et al. (1972) of the method published by Curry (1968), using a gas chromatograph equipped with an electron capture detector. Quantitation was achieved by the use of calibration curves based on trifluperidol as internal standard. A further confirmation of the identity of CPZ and its metabolites was given by thin layer chromatography (TLC) in several systems (Turano et al., 1973; Wechsler et al., 1967).

RESULTS

The levels of CPZ and CPZ-sulphoxide (CPZ-SO) in ng/ml were in two independent determinations:

Patient		A	B
Drug response		good	poor
CPZ	plasma	82, 122	212, 381
	CSF	4, 8	15, 16
CPZ-SO	plasma	71, 109	98, 101
	CSF	8, 22	201, 296

In the plasma of patients A and B we also found small amounts of mono-, and didesmethyl-CPZ which could, however, not be quantitated at that time. None of these compounds was detected in the CSF samples, which means that if they were present their concentrations were smaller than 10 ng/ml, which is the detection limit. The samples from patient C gave no gas chromatographic peaks with the same retention time as CPZ or its mentioned metabolites. The drugs other than CPZ given to patients A and B (levomepromazine, orphenadrine, and propiomazine) did not interfere with the analyses. Thus the peaks found in the gas chromatograms from patients A and B are considered to represent CPZ, CPZ-SO, mono- and didesmethyl-CPZ which was also confirmed by the TLC.

DISCUSSION

The most striking finding is the high concentration of CPZ-SO in the CSF of the poor responder (see table). While the CSF/plasma concentration ratios for CPZ are of the same order of magnitude in the poor and the good responder these ratios for CPZ-SO are very different. The predominance of the CPZ-SO in the CSF of the poor responder is noteworthy when considering the fact that CPZ-SO presumably had no antipsychotic activity in contrast to CPZ, mono- and didesmethyl-CPZ, CPZ-N-oxide and 7-hydroxy-CPZ, and probably several other metabolites (Manian et al., 1965; Manian et al., 1971; Nybäck & Sedvall, 1972). Sakalis and co-workers (1972, 1973) reported poor responders with very high plasma levels of CPZ-SO in contrast to good responders with high levels of CPZ and 7-hydroxy-CPZ (see also Mackay et al., 1974). They comment, that a patient producing mainly active metabolites would respond better than one producing inactive metabolites although the plasma levels of CPZ itself might be similar. The present plasma levels alone give no explanation for the different responses, which, however, could be explained when considering also the CSF levels, which might better reflect the concentrations at the brain receptors. The reasons are not clear for the high levels of CPZ-SO in the CSF of patient B, which do not fit the common model with equal concentrations in plasma water and CSF when corrected for plasma protein binding.

As far as we know no previous investigation on the correlation between clinical effects and CSF levels of CPZ and its metabolites has been reported. These early results of a systematic study on this topic seem interesting enough to draw the attention of others to the possible clinical value of CSF levels of psycho-active drugs.

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