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STUDIES ON THE PASSAGE OF NOMIFENSINE AND ITS METABOLITES THROUGH THE BLOOD-CEREBROSPINAL BARRIER IN DOGS

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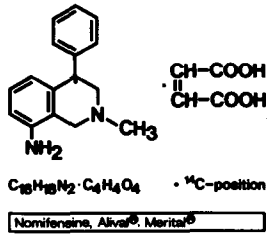
Introduction

Nomifensine (8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline maleate), an antidepressant not derived from conventional tricyclic structures, and its metabolites are present mainly in conjugated form during passage through the body.



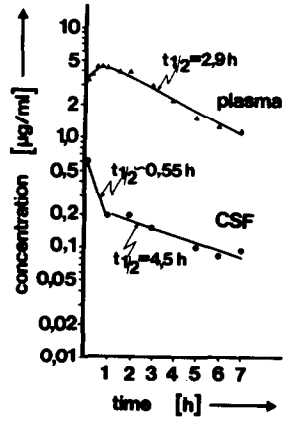
Apart from acid-stable O-glucuronides of the metabolites, the conjugates consist largely of acid-labile N-glucuronides of the unchanged parent compound and of its metabolites (1-6).

It is assumed that polar substances cannot pass the blood-cerebrospinal barrier or can pass it only with difficulty (7). The aim of these studies was therefore to clarify whether or not nomifensine and/or its metabolites are found in the brain. The medium used for the studies was the cerebrospinal fluid of dogs.

Sample Evaluation

Radioactivity measurements: Liquid scintillation

Metabolism studies: Thin layer chromatography. The very low concentrations of radioactivity in the cerebrospinal fluid permit only semiquantitative evaluation.

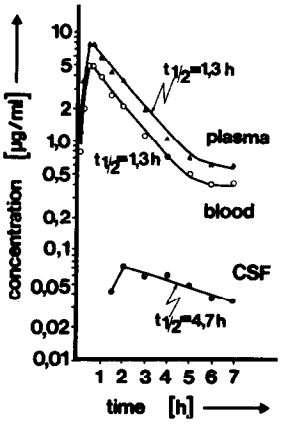


concentrations in plasma and CSF of a dog after iv. administration of 5.0 mg Nomifensine/kg body weight

Results

Pharmacokinetics: Eight minutes after intravenous administration of 5.0 mg nomifensine per kg body weight, the concentration in the plasma was 3.4 µg/ml and it reached a maximum of 4.4 µg/ml 45 minutes after administration. The concentration decreased with a biological half-life of 2.9 hours. The highest concentration in the cerebrospinal fluid was measured eight minutes after injection and, at 0.58 µg/ml, was approx. 1/6 of the comparable plasma level. The elimination was biphasic with half-lives of 0.5 hours and 4.5 hours.

After oral administration of 5.7 mg nomifensine per kg body weight, the rapid absorption led to a maximum plasma level of 8.8 µg/ml 45 minutes after administration. A

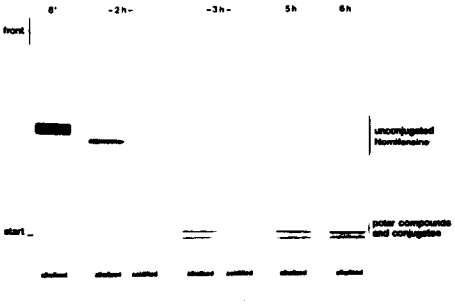


concentrations in plasma, blood and CSF of a dog after po. administration of 5.7mg Nomifensine/kg body weight

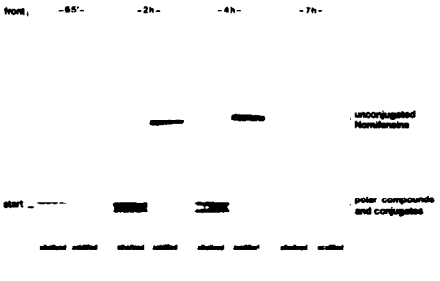
half-life of 1.3 hours was determined for the subsequent concentration decrease. The levels measured in the blood were always approx. 1/3 lower than the plasma levels determined at the same times.

65 minutes after oral administration, the concentration measured in the cerebrospinal fluid was, at o.o49 µg/ml, less than 1/loo of the corresponding plasma level. After rising to o.o81 µg/ml at 2 hours after administration, the concentration then decreased with a half-life of approx. 4.7 hours.

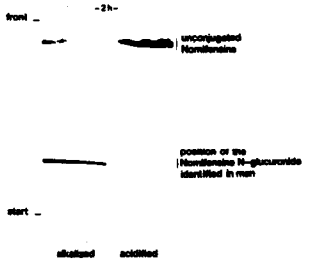
Metabolism: Thin layer chromatography showed that, to begin with, virtually only free nomifensine was found in the cerebrospinal fluid after intravenous administration. As the study progressed, both increasing amounts of metabolites and relatively large quantities of acid-labile conjugate were also found.



thin-layer autoradiograms of CSF samples after iv administration of Nomifensine



thin-layer autoradiograms of CSF samples after po administration of Nomifensine



thin-layer autoradiograms of the 2-hour CSF sample (p.o.) with a second mobile phase

After oral administration, a considerable amount of acid-labile conjugate was detected in all the samples.

A second thin layer chromatographic separation system showed clearly the acid-labile behaviour of the polar components in the cerebrospinal fluid.

Discussion and Summary

The studies have demonstrated the presence of nomifensine and its metabolites in the cerebrospinal fluid. From these studies, it is not possible to give a definite answer as tc whether the acid labile conjugate and the metabolites reach the cerebrospinal fluid by passing the blood-cerebrospinal barrier or by metabolism of the free nomifensine after it has passed this barrier. The fact that the metabolites found in the cerebrospinal fluid were the same as those to found in the plasma points to a transition rather than to autochtonous formation in the cerebrospinal fluid.

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