On the microbial degradation of lamotrigine in activated sludge and its occurrence in wastewater and surface waters

S. Pérez[a], V. Osorio[a], H. Singer[b] and D. Barceló[a,c]

a IDAEA-CSIC, Department of Environmental Chemistry, Jordi Girona 18-26, Barcelona (Spain)
b EAWAG, Swiss Federal Institute of Aquatic Science and Technology, 8600 Dübendorf, (Switzerland)
c ICRA, Parc Científic i Tecnològic de la Universitat de Girona,Edifici Jaume Casademont, Porta A, Planta 1 - Despatx 13C/ Pic de Peguera, 15, E-17003 Girona (Spain).

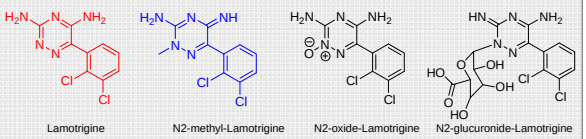
Abstract

This study describes the assessment of the biodegradation of the lamotrigine, an anticonvulsant drug, by the bacterial community in mixed liquor from a municipal STP. The UPLC analysis of the samples from the aerated batch-reactor loaded with undiluted mixed liquor showed the formation of a single metabolite. High resolution mass spectrometry (QToF) pointed towards conversion of lamotrigine through a methylation pathway. In on-going studies we are currently investigating whether this microbial transformation product is chemically identical to the N2-methylated metabolite formed in humans.

Detection of transformtion products of environmental contaminants in the environmental matrices is a challenging task because not only are they present in very low concentrations but they are also mixed with complex matrices that interfere with the detection. Therefore, Orbitrap mass spectrometry was used in a monitoring survey of lamotrigine, its metabolites and the identified TP of the present work. In the surface waters from the river Rhine (Basel, Switzerland) and in effluent samples of Swiss WWTPs that discharge into this river, lamotrigine was detected along with its human metabolites and the proposed methylated TP.

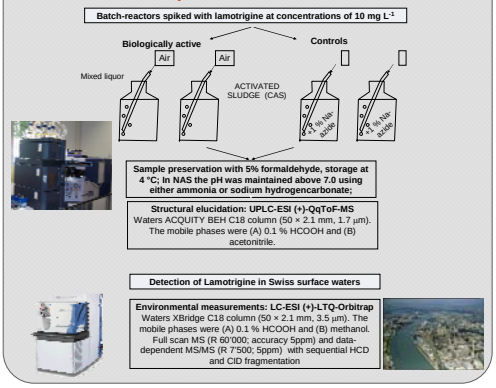
Background

Lamotrigine (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine) is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder, chemically unrelated to any currently marketed antiepileptic drugs. It is extensively metabolized in humans to produce predominantly the N2-glucuronide and to a minor extent the N2-methyl-lamotrigine. The N2-methylated metabolite has been found to have cardio-active properties. The metabolism of lamotrigine in rats, apart from other metabolites, yields N2-oxide-lamotrigine. Since most pharmaceuticals used in human medicine are eventually disposed of with the sewage, wastewater treatment facilities play a key role in removing drugs from the waste stream, thus preventing them from reaching the receiving water bodies. Recently, a U.S. study revealed the environmental occurrence of lamotrigine and its N2-glucuronide with mean concentrations in wastewater of 488 and 209 ng/L, respectively. However, they did not monitor transformation products of lamotrigine that can potentially be generated during the biological wastewater treatment.

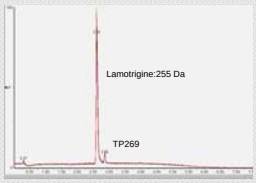


Lamotrigine | N2-methyl-Lamotrigine | N2-oxide-Lamotrigine | N2-glucuronide-Lamotrigine

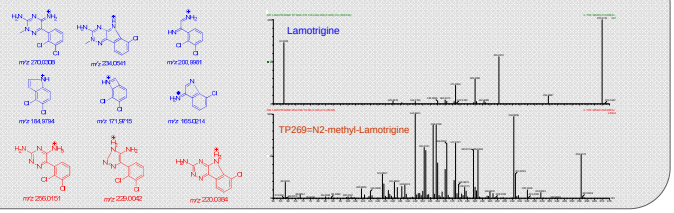
Experimental section



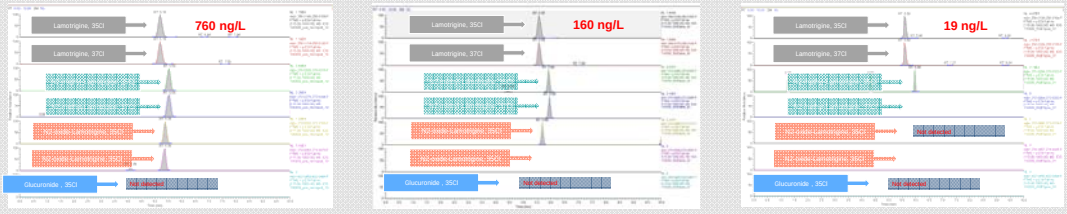
Lamotrigine-Transformation Product



(+)ESI-MS/MS spectra of lamotrigine and its transformation product at ce 30 eV



Detection of lamotrigine, its metabolites and its TP in wastewater and surface waters in Swiss waters



- WWTP effluent with high lamotrigine concentration
- River Glatt – high fraction of treated waste water
- River Rhine in Basel – low fraction of treated waste water, large river

Conclusions

- Removal of parent pharmaceuticals in WWTPs does not mean complete elimination from wastewater effluents
- New TPs can be formed; in our case the identified structure of the TP matches with the structure of a human metabolite of lamotrigine
- One human metabolite and one TP were detected in the surface waters from the river Rhine (Basel, Switzerland) and in effluent samples of Swiss WWTPs that discharge into this river

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