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THERAPEUTICS

Success of tardive electroconvulsive therapy sessions after loxapine-induced malignant syndrome in the context of very poor metabolisation

Succès d'une cure de sismothérapie tardive dans un cas de syndrome malin à la loxapine associé à une cinétique d'élimination très ralentie

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Summary We report the success of tardive electroconvulsive therapy in a case of loxapine malignant syndrome with catatonia. Loxapine and its metabolites were measured in biological samples by liquid chromatography coupled to tandem mass spectrometry. Genes were studied by sequencing and quantitative polymerase chain reaction (PCR). Plasmatic drug concentrations showed a supratherapeutic concentration of loxapine with a very low 8-hydroxyloxapine/loxapine ratio (range from 0.32 to 0.66, normal value > 2 for 100 mg) and a very long elimination half-life of loxapine (half-life > 140 h, normal value from 1 to 4 hours). We tried to explain this kinetics by exploring the main pharmacogenes implicated in the metabolism of loxapine. No genetic abnormality for *CYP1A2* was observed. The study of associated treatments showed the potential contribution of valproate. Pharmacokinetics and pharmacogenetics

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investigations revealed a blockade of the CYP1A2 metabolic pathway without genetic abnormalities, probably due to valproate co-medication. Toxicological monitoring of loxapine and its metabolites helped to explain the persistence of symptoms and to adapt the therapeutic management.

MOTS CLÉS
Sismothérapie ;
Loxapine ;
Syndrome malin des neuroleptiques ;
Pharmacocinétique ;
Pharmacogénétique ;
Phénoconversion

Résumé Nous avons documenté pharmacologiquement le succès d'une cure de sismothérapie tardive dans un cas de syndrome malin à la loxapine, avec catatonie. Les dosages de la loxapine et de ses métabolites ont été réalisés en chromatographie liquide couplée à la spectrométrie de masse en tandem. L'étude des gènes a été réalisée par séquençage et la *polymerase chain reaction* (PCR) quantitative. L'analyse des concentrations a mis en évidence un surdosage en loxapine avec un ratio 8-hydroxyloxapine/loxapine effondré (0,32—0,66, ratio normal > 2 pour 100 mg) et une demi-vie d'élimination de la loxapine extrêmement allongée (demi-vie > 140 h pour une valeur normale entre 1 et 4 h). Nous avons essayé d'expliquer cette cinétique en explorant les principaux gènes impliqués dans le métabolisme de la loxapine. Aucune anomalie génétique pour le gène *CYP1A2* n'a été retrouvée. L'étude des traitements associés a mis en évidence la contribution probable de l'acide valproïque. Les investigations pharmacocinétiques et pharmacogénétiques ont mis en évidence un blocage de la voie métabolique du cytochrome CYP1A2 sans anomalie génétique, probablement imputable au traitement associé par l'acide valproïque. Le suivi toxicologique a permis d'expliquer la persistance des symptômes et d'adapter la prise en charge thérapeutique.

Abbreviations

BMI	body mass index
GGT	gamma glutamyltransferase
LC-MS/MS	high performance liquid chromatograpy coupled with tandem mass spectrometry
PCR	polymerase chain reaction
SGOT	serum glutamo-oxaloacetate transferase
SGPT	serum glutamopyruvate transferase
TDM	therapeutic drug monitoring

Introduction

In general and for drugs in psychiatry in particular, therapeutic drug monitoring (TDM) is required because patients differ in their ability to absorb, distribute, metabolize and excrete drugs due to concurrent disease, age, concomitant medication or genetic peculiarities. Consensus guidelines are available for many drugs but not for all, and although therapeutic ranges are defined for chronical therapy, values to take medical decision in particular clinical situation such acute care and against adverse drug reactions are not exhaustively defined [1].

Loxapine (2-chloro-11-[4-methyl-1-piperazinyl]dibenz [b,f][1,4]oxazepine) is a dibenzoxazepine first-generation antipsychotic drug, used to treat schizophrenia, psychotic disorders and acute agitated and aggressive behavioural disturbances.

The usual dosage of loxapine ranges between 75 and 200 mg/day. Some patients may require higher doses, which should not exceed 600 mg/day. When acute symptoms are stabilized, the physician should attempt to reduce the treatment to reach the minimal effective dosage. Following oral administration, loxapine is extensively metabolized in the liver into numerous metabolites. In humans, the metabolites accounting for up to 70% of the total dose are formed through the following metabolic pathways: hydroxylation to form 8-OH-loxapine (54%) by CYP1A2 and 7-OH-loxapine (16%) by CYP2D6, desmethylation to form amoxapine (13%) by CYP3A4; minor metabolites are 7-OH-amoxapine, 8-OH-amoxapine and loxapine N-oxide (Fig. 1) [2—4]. 7-OH-loxapine has dopaminergic and serotoninergic properties and may be presumed to have similar pharmacologic properties than loxapine, whereas 8-OH-loxapine should have negligible activity because of its very poor affinity to dopamine and serotonine receptors. Amoxapine is as itself an antidepressive agent with both noradrenergic and serotonine presynaptic reuptake inhibitory properties. Neurologic adverse effects of amoxapine (convulsive strikes) are rare.

The plasma half-life is 1 to 4 h for loxapine, around 8 h for 8-hydroxyloxapine, and 36 to 48 h for 8-hydroxyamoxapine. The adverse effects profile of loxapine is comparable to

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