Clinical Note

Life-Threatening Dextromethorphan Intoxication Associated with Interaction with Amitriptyline in a Poor CYP2D6 Metabolizer: A Single Case Re-Exposure Study

Patrice Forget, MD, Bernard le Polain de Waroux, MD, Pierre Wallemacq, MD, PhD, and Jean-Luc Gala, MD, PhD

Department of Anesthesiology (P.F., B.l.P.d.W.), Department of Clinical Chemistry (P.W.), and Department of Genetics (J.-L.G.), Center for Applied Molecular Technologies, Université Catholique de Louvain, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Abstract

*We report a case of life-threatening intoxication and a controlled re-exposure study to dextromethorphan. A 60-year-old man developed postsurgical neuropathic cervical pain treated by hydromorphone, gabapentin, clonazepam, and amitriptyline. He received a dextromethorphan preparation for a catarrhal syndrome. Two days later, he was admitted into an emergency department in a profound coma. Thirty-six hours later, after withdrawal of all drugs, the situation normalized. A genotyping for UDP-glucuronyltransferase 1A1 and CYP2D6 was followed by a re-exposure study. During the three days, vital parameters and side effects of drugs were prospectively recorded. The second day, dextromethorphan was introduced. No significant impairment in parameters nor influence on analgesic efficacy were noted. Dextromethorphan concentrations suggested an accumulation without reaching any steady state. Somnolence was noted for plasma concentrations around 100 ng/mL. The CYP2D6*4 variant leading to a poor metabolizer phenotype was found. Moreover, this phenotype was potentially aggravated by amitriptyline intake. This study allowed the identification and the confirmation of the cause of the coma. In conclusion, it is probably wise to recommend avoiding dextromethorphan in patients taking tricyclic antidepressants or another inhibitor of CYP2D6. Drug–drug interactions are probably underdiagnosed and underreported, and drugs considered as safe may induce serious complications.* J Pain Symptom Manage 2008;36:92–96. © *2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Dextromethorphan, amitriptyline, interaction, CYP2D6

Address correspondence to: Bernard le Polain de Waroux, MD, Department of Anesthesiology, Cliniques Universitaires Saint-Luc, av. Hippocrate 10, 1200 Brussels, Belgium. E-mail: lepolain@anes.ucl.ac.be

Accepted for publication: September 18, 2007.

Introduction

Polymorphisms of genes coding for drug-metabolizing enzymes and drug–drug interactions may expose patients either to lack of efficacy or to drug-induced toxicity and serious

0885-3924/08/$–see front matter
doi:10.1016/j.jpainsymman.2007.09.006

adverse effects, which can be life-threatening.[1] The dramatic progress achieved recently in pharmacogenetics/pharmacokinetics allows better understanding of some of the difficulties observed in clinical practice.

Cytochrome P450 CYP2D6 is one of the best-studied polymorphic genes of pharmacologic interest.[1] Frequency of polymorphism includes 1%−10% ultrarapid metabolizers. This condition has been recently reported to be associated with codeine intoxication.[2] The poor metabolizer phenotype is mostly inherited as an autosomal recessive trait and has been reported to be 5%−13.5% in White populations, but as low as 0%−1% in Asians.[1] The metabolism of numerous drugs is affected by the CYP2D6 polymorphism. These include antiarrythmics, tricyclic antidepressants, opioids, antipsychotics, β-adrenoreceptor antagonists, and dextromethorphan (DEX). Patients with a poor-metabolizer phenotype are at risk of increased plasma concentration and toxicity.

DEX is widely used for cough and less frequently for pain treatment. It is considered as safe for most patients. Its metabolism is extensively described, particularly in the pharmacogenetic context of poor and extensive metabolizers.[3] CYP2D6 is responsible for *O*-demethylation of the majority of DEX to dextrorphan (DXO) and CYP3A4/5 is involved in *N*-demethylation of DEX to 3-methoxymorphinan. DXO and 3-methoxymorphinan concentrations provide a reliable index of CYP2D6 and CYP3A4/5 activity in phenotyping studies.[3] DXO undergoes further glucuronidation, producing DXO-glucuronide.

Amitriptyline is a well-known tricyclic antidepressant prescribed for chronic pain syndromes. Its major metabolic pathway is mediated by CYP2C19 and CYP2D6. Amitriptyline is primarily demethylated to nortriptyline and then hydroxylated by CYP2D6 to 10-OH-nortriptyline.[4] It has been recently shown that side effects can be related to genotype.[5] Amitriptyline has been proven to inhibit CYP2D6 competitively in human liver microsomes,[6] possibly impairing the dextromethorphan-*O*-demethylation.

No clinically relevant interaction has been described between amitriptyline and DEX. However, a few DEX intoxications were reported at therapeutic doses. These were attributed to innate (deficiency of CYP2D6) or acquired (fluoxetine-related CYP2D6 inhibition) poor metabolism.[7–9]

We report here a case of life-threatening DEX intoxication potentially due to an interaction with amitriptyline in a poor metabolizer-patient treated for acute cough and chronic pain. Because of several implications (diagnostic confirmation, optimization of analgesia, and clinical research), a well-controlled re-exposure protocol was proposed to the patient.

Case Report

The history of this 60-year-old man is marked by surgery 13 years ago for a malignant lingual tumor. Some months after surgery, he developed a neuropathic cervical pain, which was treated with an opioid—extended-release hydromorphone 48 mg twice daily (Palladone®, Mundipharma, Mechelen, Belgium). Pain was not adequately controlled and other medications were added: gabapentin 600 mg four times a day (Neurontin®, Pfizer, Brussels, Belgium), clonazepam 1 mg (Rivotril®, Roche, Brussels, Belgium), and amitriptyline 50 mg (Redomex®, Lundbeck, Brussels, Belgium) in the evening. The patient was also taking insulin for diabetes mellitus 25 IU subcutaneous (SC), in the morning and 11 IU SC in the evening (Mixtard 30/70®, Novo Nordisk, Brussels, Belgium). With this combined treatment, pain relief was quite good.

He developed a catarrhal syndrome, treated with paracetamol (Dafalgan®, Bristol-Myers Squibb, Brussels) 4 g per day and acetylsalicylic acid (Sedergine®, Bristol-Myers Squibb, Brussels). One day later, he received from his pharmacist a DEX preparation (dextromethorphan bromhydrate 15 mg, guaifenesin 50 mg per 5 mL, Acatar®, SMB, Brussels, Belgium) to take three times a day. After the fourth dose of DEX, he became very somnolent, and 12 hours later, he was admitted into an emergency department for profound coma. Punctiform pupils were noted.

Because of suspicion of drug-induced toxicity, all analgesic treatment was stopped. The situation normalized 36 hours later. His pain treatment was then reintroduced with lower doses of hydromorphone—24 mg three times per day.