

CASE REPORT

Hazardous Drug Diversion of Valproate from a General Practitioner to his Patient's Dog

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Abstract General practitioners are key stakeholders in good prescribing practices. More than half of patients have at least one unintended medication discrepancy upon hospital admission, some of which have the potential to cause severe discomfort or clinical deterioration. We report a case of a drug mistakenly administered to a 66-year-old man with cirrhosis and chronic alcoholism. Based on his regular prescription, he received 1 g/day of valproate during a hospitalization for cardiac valve surgery. This anticonvulsant was initially prescribed by his general practitioner for his epileptic dog and has been added to his own prescription to be covered by the French national health insurance. The aim of this article is to emphasize that general practitioners, physicians, and pharmacists have a major role to play in preventing the diversion of prescription drugs and limiting the risk of adverse drug events.

Key Points

Prescription drug diversion is a serious public health problem that can lead to severe adverse consequences.

Medication reconciliation is a strategy requiring a complete review of all the medication taken by a patient during his/her hospitalization (admission, transfer, and discharge).

Physicians and pharmacists have a major role to play in preventing the diversion of prescription drugs and can be helped by medication reconciliation.

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Introduction

The diversion of prescription drugs is a serious public health problem that can lead to severe adverse consequences such as overdose, admission to an emergency department, or death. The most affected drugs are opioid analgesics (hydrocodone, oxycodone), central nervous system depressants (alprazolam, diazepam), or stimulants (amphetamine) [1]. Lifestyle and prescription drug diversion can increase the risk of adverse drug events [2]. Because of a prescription given to the physician at admission, a 66-year-old man referred for cardiac valve surgery received oral valproate during his hospitalization. This drug was not initially prescribed for him but for his epileptic dog, in accordance with his general practitioner, to benefit from the reimbursement of the drug by the French national health insurance.

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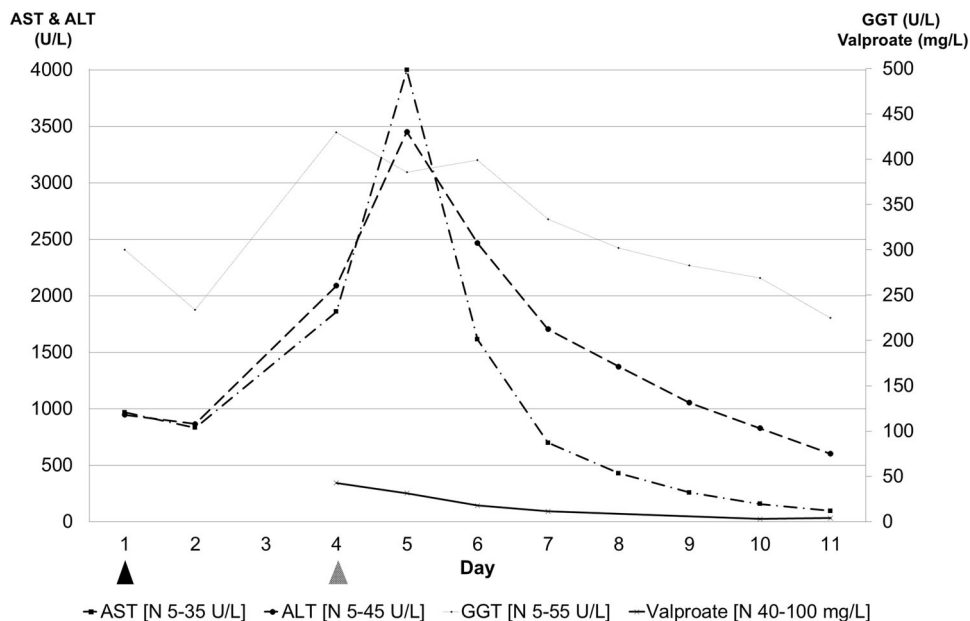
A 66-year-old man hospitalized for cardiac valve surgery was admitted to the cardiology department for acute heart failure. His past medical history included alcoholic cirrhosis (Child A6) complicated by esophageal varices for 10 years, paroxysmal atrial fibrillation for 4 years, a mildly reduced kidney function (estimated glomerular filtration rate: 60–89 mL/min/1.73 m²) and 1 year prior, he had a mitral and aortic valve endocarditis caused by *Staphylococcus epidermidis* (successfully treated with intravenous vancomycin, gentamicin, and cloxacillin). His regular prescription medication at admission included isosorbide mononitrate (24 mg/day), valproate (1 g/day), inhaled beclomethasone (400 µg/day), furosemide (125 mg/day), and vitamin supplements. Blood biochemistry evaluations revealed the following: increases in the plasma potassium level to 6.1 mmol/L (reference range 3.6–4.8 mmol/L) and troponin I level to 0.09 ng/mL (reference range <0.04 ng/mL). Plasma creatinine level was 117.6 µmol/L (reference range 40–100 µmol/L) with a moderate renal impairment (clearance calculated by the Modification of Diet in Renal Disease equation: 54 mL/min/1.73 m²). Observations revealed a heart rate of 145 beats per minute, a blood pressure of 130/81 mmHg, and a normal oxygen saturation level of 98% with supplemental oxygen therapy (nasal cannula, 2 L/min). An electrocardiogram showed a heart rate of 154 beats per minute and atrial fibrillation. Auscultation revealed crepitant rales with murmurs, hepatogastric reflux, and edema in the lower extremities. A chest X-ray showed signs of cardiogenic pulmonary edema such as cardiomegaly, unilateral pleural effusion on the right side, and peripheral edema. The patient showed a good response to intravenous furosemide. After an improvement in the initial heart failure, the valve surgery was postponed because of a progressive increase in baseline liver enzymes level without fever. At day 3, the patient confessed to physicians an excessive drinking behavior (more than 1 L of beer every day) and a daily acetaminophen consumption (8 g every day): valproate and acetaminophen were stopped. Blood toxicological analysis collected on the fourth day showed a valproate concentration of 42.8 mg/L (therapeutic range 40–100 mg/L) followed by a gradual decrease, and an acetaminophen concentration under the lower limit of quantification (Fig. 1, day 4). Liver function analysis showed that the level of gamma-glutamyl transpeptidase was increased [peak plasma level on the fourth day at 386 U/L (reference range 5–55 U/L)], as well as the levels of alanine aminotransferase and aspartate aminotransferase [peak plasma levels on the fifth day at 3997 and 3452 U/L, respectively (reference range 5–45 U/L)]. The levels of total bilirubin and conjugated bilirubin

were increased with a peak plasma level on the fifth day at 44 (reference range 1–17 µmol/L) and 16 µmol/L (reference range <3 µmol/L), respectively. Alkaline phosphatase, prothrombin time, and international normalized ratio were within normal limits. No ammonia, brain natriuretic peptide, glutathione level analysis, and liver biopsy were performed. Abdominal ultrasound showed a cirrhotic liver without bile duct obstruction. Hepatic veins were also normal. Viral infections were ruled out by blood examinations (viral hepatitis A, B, C, D, and E; human immunodeficiency and herpesviridae viruses). Intravenous administration of *N*-acetylcysteine started on day 5 (Fig. 1) and was associated with a decrease in liver enzymes that gradually returned to normal values and then were completely back to normal 1 month later. The patient admitted that valproate was not originally prescribed for him but for his dog to benefit from the reimbursement of this drug by the French national health insurances (veterinary drugs are indeed at the entire charge of the dog owner) and unfortunately the valproate was initiated upon his admission because it was noted as being one of the patient's regular prescription drugs. Investigations revealed that this practice began 6 months previously.

Discussion

Drug diversion is an illegal distribution, an abuse of prescription drugs, or a use for purposes not intended by the prescriber. It manifests itself through various forms such as illegal Internet pharmacies, prescription forgery doctor shopping, or illicit prescribing by physicians [3]. The results from the 2012 National Survey on Drug Use and Health present the prescription drug abuse as a new epidemic and people are unaware that it causes harms, deaths, and economic costs [4]. Anabolic steroids, depressants, stimulants, hallucinogens, and opioids have a high potential for diversion [5]. In USA, the non-medical use of prescription drugs concerns 20% of the population (52 million people aged 12 years and older) [6]. To thwart drug diversion, physicians are helped by the development of new tools before prescribing, such as 'prescription drug monitoring programs', even if some practitioners disagree with the idea of using it (usability, dissatisfaction, erosion of physician autonomy) [7]. Community pharmacists also use educational supports and data-sharing projects for the management of patients suspected to be at high risk for drug diversion [8, 9]. In hospitals, pharmacists are responsible for the safe use of medications by reducing the risk of adverse events through medication reconciliation. They try to obtain the most accurate list of patients' current medicines to ensure that medications being added,

Fig. 1 Evolution of biological and toxicological parameters: blood alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyltransferase (GGT), and valproate. Transaminase blood levels are represented on the *left axis*, the other parameters on the *right axis*. Markers indicate the beginning of valproate therapy (filled triangle) and valproate drug monitoring (shaded triangle)



changed, or discontinued during hospitalization are cautiously evaluated. Hospital pharmacists significantly reduced the number of medication errors (including errors of high and extreme risk) [10, 11]. The aim is to reduce medication discrepancies and to prevent future events related to drug omissions (medication taken by the patient without any mention in the medical record), drug commissions (medication present in the medical record but not taken by the patient), drug duplications, dosing errors, and drug–drug interactions [12]. At admission, our patient received by error a non-indicated drug without having benefited from medication reconciliation. Since this event, we extended medication reconciliation to cardiology and nephrology care units. Unfortunately, we have no scientific data on the diversion of prescription drugs in France, but it seems not to be a common practice, unlike opioid diversion [13, 14]. Limiting the diversion of prescription drugs requires a coordinated approach between each member of the health system: pharmacists, physicians, and general practitioners, all supported by fraud control. This coordinated approach includes equal access to electronic medical records and the provision of additional continuing education to healthcare professionals.

Conclusion

This case report highlights the imperative need to strictly control indications of home drugs administered during hospitalization and the damaging consequences of the inappropriate use of reimbursement systems. A study found

that 53.6% of patients had at least one unintended medication discrepancy upon admission, some of which had the potential to cause severe discomfort or clinical deterioration [15]. Moreover, these controls could limit adverse drug events, which represent a significant financial burden to healthcare with a US\$887 million estimated cost in 2006 in USA [16]. General practitioners, physicians, and pharmacists play a major role in this context. They could be helped by the development of medical conciliation at patient hospital admission or discharge and by new healthcare delivery processes or tools [17, 18].

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Compliance with Ethical Standards

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Conflict of interest Pierre-Marie Morice, Joachim Alexandre, Alexandre Cesbron, Marion Sassier, Sophie Fedrizzi, and Xavier Humbert have no conflicts of interest directly relevant to the content of this case report.

Consent Written informed consent was obtained from the patient for publication of this case report.

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