Cases of Liver Failure in Association with Flupirtine in the German Spontaneous Reporting Database

Thomas Stammschulte[1], Ulrich Treichel[1,2], Henry Pachl[1], Ursula Gundert-Remy[1]

[1]Drug Commission of the German Medical Association, Berlin, Germany; www.akdae.de

[2]Westmecklenburg Klinikum Helene von Bülow, Hagenow, Germany

thomas.stammschulte@akdae.de

Introduction

Flupirtine is a centrally acting, non-opioid analgesic. It is classified as a Selective Neuronal Potassium (KCNQ) Channel Opener (SNEPCO) (Figure 1). In Germany, flupirtine is approved since the 1980's for the treatment of acute and chronic musculoskeletal pain, tension headache, cancer pain, dysmenorrhea and pain following traumatologic/orthopedic surgery and injury. Flupirtine prescription increased over the years. In 2010, more than 30 million DDD (defined daily doses) were prescribed[1] (Figure 2). The Drug Commission of the German Medical Association notified healthcare professionals about reports on hepatitis in association with flupirtine in 2007[2]. Further case reports and study results were published[3;4]. However, frequency and causality of drug-induced liver injury in association with flupirtine remains under discussion[5].

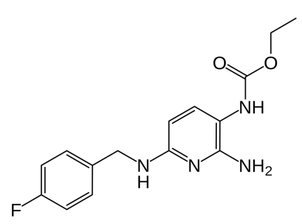

Figure 1: Structural formula of flupirtine.

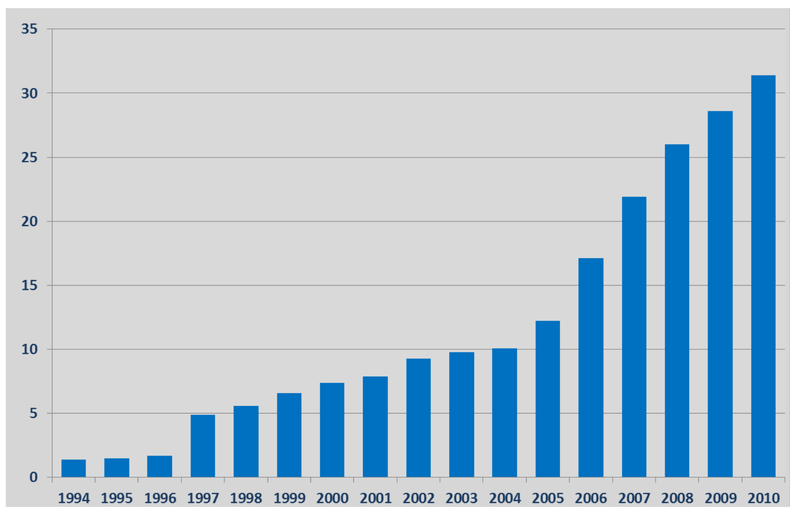

Figure 2: Prescriptions [million defined daily doses (DDD)] of flupirtine reimbursed by German statutory health insurance 1994–2010 for outpatient care.

Aim

To assess causality and to identify risk factors in cases of severe liver injury associated with flupirtine treatment in the German spontaneous reporting system.

Methods

We collected data on acute liver failure associated with flupirtine treatment from original reporting documents and database records in the German spontaneous reporting system. Cases with recorded reaction 'liver failure' or 'acute liver failure' (MedDRA Preferred term (PT)) were included. Severity was classified according to the scale by the Drug-Induced Liver Injury Network, DILIN[6]. Causality was assessed by using the CIOMS/RUCAM score[7].

Results

Between 2003 and 2011, 37 reports of acute liver failure in association with flupirtine were identified. Median age of patients was 49 years (range 28–72), 30 patients (81 %) were female (two-thirds of flupirtine prescriptions in Germany are for women) (Table 1).

Table 1: Patient characteristics, outcome of cases as recorded in the database and severity assessed by DILIN scale.

Total number of cases	**37**	
Age	49,3 years (median, min. 28, max. 72)	
Sex	30 female , 7 male	
Daily dose of flupirtine	400 mg (median, min. 100, max. 500), unknown in 7 cases	
Severity (DILIN scale)	fatal	7 (incl. 2 x LTX*)
	severe	18
	moderate-severe	6
	mild	1
	not assessable	5

* liver transplantation

In most cases, the indication was musculoskeletal pain. The dosages of flupirtine were in accordance with the product information in all cases. Median time was 61 days (range 14–365) from initiation of treatment until the reaction (Figure 3). Five patients died, in two cases liver transplantation was performed, another patient died shortly afterwards due to progressive malignant disease, in the remaining cases patients recovered or final outcome is unknown.

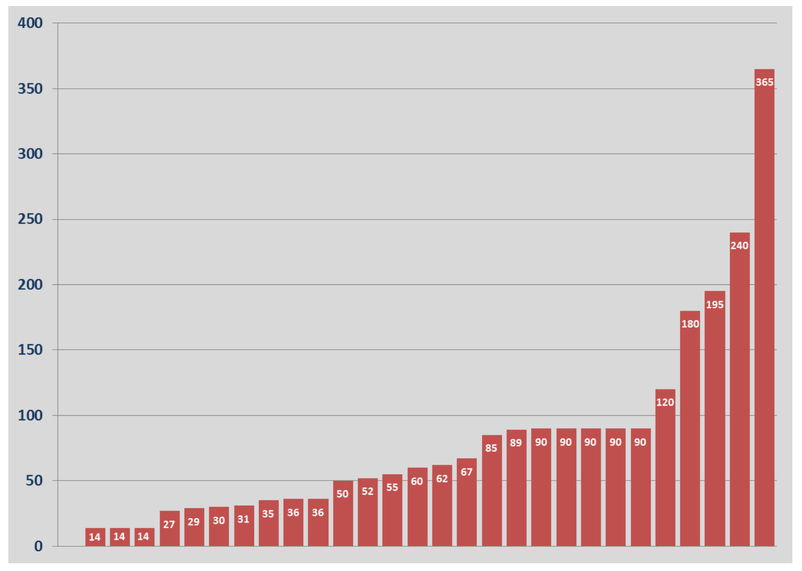

Figure 3: Interval [days] from beginning of medication with flupiritine until diagnosis of liver failure (data available for 28 of 37 cases).

The type of liver injury was hepatocellular in all except for one case with cholestatic type. Results of the causality assessment are shown in Figure 4 and presence of risk factors for drug-induced liver injury according to CIOMS score are listed in Table 2.

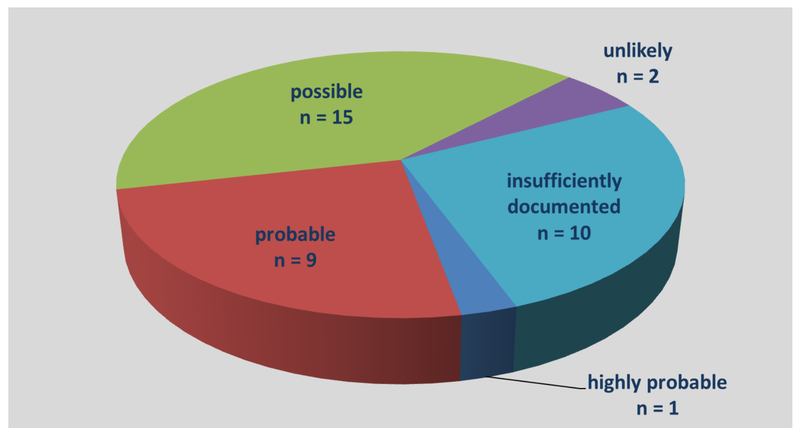

Figure 4: Results of causality assessment according to the RUCAM/CIOMS score.

Table 2: Risk factors for drug-induced liver injury and concomitant drugs in the assessed cases according to CIOMS score.

Risk factors (CIOMS score)	Number of cases
Ethanol	2
Pregnancy	none
Age of the patient ≥ 55 years	9

Alternative causes for liver injury were concomitant drugs known as hepatotoxic in 18 cases. Most of these drugs were NSAIDs (n = 11) or antipsychotics (n = 5).

List of concomitant, potential hepatotoxic drugs (n = 16) (alphabetical order)
Amitriptyline (3), Baclofen, Celecoxib, Citalopram, Dexibuprofen, Diazepam, Diclofenac, Esomeprazole, Etoricoxib, Ibuprofen (5), Naproxen, Paracetamol (2), Paroxetine, Ranitidine, Tolperisone, Venlafaxine

Conclusion

The analysis of the cases results in a signal indicating that flupirtine may cause serious hepatotoxicity. Possible risk factors for liver failure in association with flupirtine are longer duration of therapy and concomitant medication with other potential hepatotoxic drugs. The results of the severity assessment suggest that the diagnosis liver failure was probably not correct in seven cases since liver injury was less severe. However, the total number of reported cases of liver failure in association with flupirtine may even be underestimated since not all cases with documented liver injury in the database were assessed with regard to criteria for liver failure. We strongly suggest that the frequency of drug-induced liver injury associated with flupirtine is investigated in a prospective study to allow proper risk-benefit assessment for this drug.

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