Letters to the Editors

Limited adherence to safety instructions in drug leaflets

Drug effects are not solely determined by the pharmacological properties of the active substance, but also depend heavily on the way it is used in practice by health professionals and patients. Non-adherence to instructions for use seems to have contributed to the withdrawal of drugs such as troglitazon, mibefradil, and most recently cerivastatin [1–3]. Hepatotoxicity and myopathy are two rare but serious side-effects of statins. Myopathy can lead to a life threatening rhabdomyolysis. Product labelling of statins advises to monitor hepatic function and creatinine kinase (CK) concentrations (especially in patients who are experiencing muscle pain), because this may prevent progress of these drug-induced complications. The objective of the present study was to estimate the incidence of CK and hepatic function measurements in a cohort of patients starting with a statin, and to evaluate whether this was influenced by the withdrawal of cerivastatin.

From eight community pharmacies located in Tilburg, the Netherlands and surroundings, patients starting with a statin during the period December 2000–April 2001 (period 1), or during the period August 8, 2001–October 2001 (period 2) were selected. Period 2 was chosen after the withdrawal of cerivastatin. Date of filling the prescription was the index date. Age, gender, statin, prescribed dosage, and relevant concomitant drug use were obtained for all patients. From the regional clinical chemistry laboratory, which performs measurements for in- as well as outpatients, the number of hepatic function and CK measurements was determined during a 3 month follow-up period after the index date.

Five hundred and thirty patients were included. Any clinical chemistry measurement during follow-up was performed in 54.2% (287) of all patients; CK levels were checked in 13.0% (69) of the patients while hepatic function tests were performed in 22.3% (118) of all patients. There was no difference in these frequencies before, and after the withdrawal of cerivastatin (Table 1).

Gender, age, standardized dosage, interacting concomitant drug use, and CK-inducing concomitant drug use did not cause significant deviations of these outcomes. Only 5.3% (1) of the patients starting with cerivastatin was checked for CK compared with 13.3% (68) of the patients using other statins (RR 0.40 (95% CI 0.06, 2.70)). In contrast, any clinical chemistry measurement and hepatic function were determined more frequently in cerivastatin starters compared with other statin starters: RR 1.48 (95% CI 1.16, 1.90) respectively RR 3.04 (95% CI 2.08, 4.47).

This study shows that, in daily medical practice, adherence to drug prescribing guidelines to perform clinical chemistry measurements is limited. The withdrawal of cerivastatin has not led to an increase in hepatic function- and CK measurements. Cerivastatin was taken off the market because available evidence (mainly case reports) suggested a higher frequency of serious side-effects in comparison with other statins [4]. It is remarkable that CK was less frequently checked in patients using cerivastatin while hepatic function was more frequently measured in this study. It is important to recognize that the population was limited to 530 patients with only 19 starters of cerivastatin. The strength of this study was the conductance in daily practice. The risk of losing patients during follow-up was minimized because in The Netherlands outpatients usually visit the same pharmacy [5], and all clinical chemistry testing was concentrated in one laboratory.

Overall it is important to realize that a drug is not a chemical entity alone but comes along with instructions for patients and prescribers in order to optimize the benefit-harm balance. Strategies for adherence to such instructions should be developed and implemented.

Table 1 Incidence of CK, hepatic function or any clinical chemistry measurement during 3 months of follow-up

Variables	*CK measurement (%)*	*RR (95% CI)*	*Hepatic function measurement (%)*	*RR (95% CI)*	*Any clinical chemistry (%)*	*RR (95% CI)*
All statins ($n = 530$)	13.0		22.3		54.2	
Other statins ($n = 511$)	13.3	1.00	20.7	1.00	53.2	1.00
Cerivastatin ($n = 19$)	5.3	0.40 (0.06, 2.70)	63.2	3.04 (2.08, 4.47)	78.9	1.48 (1.16, 1.90)
Before withdrawal ($n = 369$)	13.3	1.00	23.6	1.00	53.4	1.00
After withdrawal ($n = 161$)	12.4	0.94 (0.58, 1.52)	19.3	0.82 (0.57, 1.18)	55.9	1.05 (0.89, 1.24)

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