The Weber-curve pitfall: effects of a forced introduction on reporting rates and reported adverse reaction profiles

• Linda de Graaf, Mariette A. Fabius, Willem L. Diemont and Eugène P. van Puijenbroek

Pharm World Sci 2003; 25(6): 260–263.

L. de Graaf (correspondence, e-mail: l.degraaf@lareb.nl), **M.A. Fabius, W.L. Diemont** and **E.P. van Puijenbroek:** Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, The Netherlands

Key words
Adverse drug reaction
Omeprazole
Pharmacovigilance
Weber-effect

Abstract
Background: In May 1999 Losec® MUPS (MUPS) were granted a marketing authorisation in the Netherlands, followed by the withdrawal of the Losec® capsules (capsules) in September 1999. Both formulations contain omeprazole as active substance. This forced switch resulted in a large number of spontaneous reports of adverse drug reactions (ADRs) to the Netherlands Pharmacovigilance Centre Lareb.
Methods: We calculated and compared the reporting rate of both formulations and grouped the reported adverse reactions into system and organ classes (SOCs) in order to analyse possible differences in the type of reported ADRs.
Results: Lareb received 480 reports on omeprazole formulations between May 1997 and December 2000. A quarter of the reports concerned a decrease in therapeutic effect. The reporting rate on MUPS showed a sharp rise after withdrawal of the capsules, but did not differ significantly from the reporting rate on the capsules. A comparison of the type of reported ADRs showed differences in six SOCs. Elimination of the reports concerning a decreased therapeutic effect reduced the number of different SOC reporting rates. Certain gastrointestinal complaints were reported more frequently as an ADR of MUPS.
Conclusion: The forced switch caused an increase in reports resembling an early Weber effect rather than a decrease in safety of the newer formulation. However, our analysis cannot exclude differences in pharmacokinetic, pharmacodynamic or safety characteristics.

Accepted April 2003

Introduction

In May 1999 the Dutch Medicine Evaluation Board granted a marketing authorisation for Losec MUPS® (MUPS). In September the same year, Losec capsules® were withdrawn from the market, although a certain amount remained available via parallel import. This forced switch from the capsule to the MUPS formulation evoked a great deal of media attention and even questions in the Dutch parliament. Losec MUPS® (multiple unit pellet system) are tablets consisting of more than one thousand enteric-coated micro-pellets. The claimed advantage of this formulation is that it can be administered either as a whole or dispersed in water.

The active substance in the capsules as well as in the MUPS is omeprazole. Omeprazole inhibits H^+/K^+-ATPase in the parietal cell in the stomach. Omeprazole also inhibits the basal and stimulated gastric-acid production[1,2]. The therapeutic indications of omeprazole, in both capsules and MUPS, include treatment and/or prevention of duodenal or ventricular ulcers, reflux oesophagitis, gastro-oesophageal reflux and dyspepsia.

Taking into account the similar active substance and therapeutic indications, we assumed that the benefit-risk ratio of MUPS is similar to the benefit-risk ratio of the capsules. One abstract of a clinical study has been published that compared capsules and MUPS for the treatment of ulcerative oesophagitis[3]. Capsules and MUPS were equally effective in grades two to four ulcerative oesophagitis at four and eight weeks, and were equally well tolerated. Another study has shown pharmacokinetic bioequivalence (area under the curve and maximum concentration) between MUPS 10, 20 and 40 mg and capsules of corresponding strengths[4].

The Netherlands Pharmacovigilance Centre, Lareb, collects and analyses reports of adverse drug reactions (ADRs) on behalf of the Dutch Medicines Evaluation Board. Physicians and pharmacists report ADRs to Lareb, but are not obliged to do so. All ADRs reported to Lareb should be considered as *suspected* adverse drug reactions. A causal relationship is not always demonstrated[5].

The forced switch from capsules to MUPS resulted in a large number of spontaneous reports. A substantial number concerned a decrease in therapeutic response. Taking into account the number of reports and the nature of the reported ADRs, the forced nature of the switch and the assumed similar benefit-risk ratio, we decided to study these reports in more detail. The aim of the study was to analyse whether the sharp rise in adverse event reporting was justified by differences in adverse reaction profiles between both formulations, or whether the rise was due to a so-called Weber effect, which decribes a slow rise in ADR reports after the marketing of a new drug. The number of reports increases until two years after the introduction and declines thereafter[6].

Methods

First of all, the reporting rates of ADRs of the capsules and MUPS were compared. To mark the periods with different availability of both formulations, we defined three time windows:

1. capsules only (01-05-1997 to 30-04-1999, an arbitrarily chosen two-year period)
2. capsules and MUPS (01-05-1999 to 31-08-1999)
3. MUPS only (01-09-1999 to 31-12-2000, the data collection closure)

Within these windows, the reporting rate was calculated as the number of reported adverse events per month.

The reported ADRs were classified according to the World Health Organisation (WHO) adverse drug reaction terminology and consequently grouped into system and organ classes (SOC)[7], in order to analyse whether there are differences between capsules and

Table 1 *Average number of reports per month per time window*

		Capsules only 24 months	Capsules and MUPS 4 months		MUPS 16 months	
	Capsules	Capsules	MUPS	Capsules	Capsules	MUPS
Number of reports	n_1	162	31	37	50	200
Number of patients	n_2	121	18	22	33	146
Average reporting rate	n_1/month	6.75	7.57	9.25	3.13	12.5

MUPS in the reported ADRs. The ADRs 'therapeutic response decreased' or 'lack of efficacy' are only applicable to patients switching from capsules to MUPS and can therefore not be reported for the capsules. Hence, a second analysis was performed, with the exclusion of these two ADRs.

Statistical analyses (Pearson χ^2, 2-sided Fisher's exact test and Student's *t*-test) were performed with SPSS 10.0 for Windows and GraphPad Instat (version 3.05). A *P*-value of < 0.05 was considered as statistically significant.

Results

Between May 1997 and December 2000 Lareb received 480 reports on capsules or MUPS, concerning 336 patients (Table 1). Of the three periods, the last one may include delivery of an uncertain amount of capsules due to stock or parallel import. Remarkably, more than a year after the withdrawal of the capsules, Lareb still received reports of ADRs related to this formulation.

We compared the capsule-related reports in the first time window with the MUPS-related reports in the third time window. Despite the initial rise in reported ADRs, the difference between the reporting rates of the capsules and the MUPS was not statistically significant (χ^2 statistic test, df = 2; $P = 0.12$) between the different time windows.

A comparison between all capsules and MUPS related reports (2-sided Fisher's exact test) revealed statistically significant differences for the SOCs and reported ADRs: 'body as a whole and general disorders', 'gastro-intestinal disorders', 'musculoskeletal disorders', 'psychiatric disorders', 'skin and appendages' and 'special senses-other disorders'. Furthermore, there were significant differences in reported ADRs: 'myalgia' and 'alopecia' were reported more often with capsules, whereas 'dyspepsia' and 'nausea' were reported more frequently with MUPS. Finally, the difference in reports concerning a decreased therapeutic response was statistically significant. This ADR and 'lack of efficacy' reflected 23.6% of all reported ADRs with MUPS, and were therefore likely to substantially affect the adverse event profile of MUPS. It should, however, be realised that it is unlikely that these ADRs would be reported in relation to the use of the capsules, since these were not preceeded by another formulation. For this reason a second analysis was performed after elimination of these terms (Table 2).
Since both 'therapeutic response decreased' and 'lack of efficacy' are classified in the SOC 'body as a whole – general disorders', the greatest change is seen in this SOC. Statistically significant differences between capsules and MUPS were now reduced to the SOCs 'gastro-intestinal disorders', 'musculoskeletal disorders', skin and appendages disorders' and 'special senses-other disorders'. The ADRs 'upper abdominal pain', 'dyspepsia', 'nausea', 'vomiting' and 'pyrosis' have been reported more frequently as an ADR of MUPS. 'Alopecia' was reported more often as an ADR of capsules.

We observed no differences in mean age between patients reporting a decrease in or lack of efficacy and patients reporting other ADRs. The male–female ratio differed significantly: men reported more 'therapeutic response decreased', whereas women reported more other ADRs (Table 3).

Discussion

The incidence of capsule-related reports seemed lower than the incidence of MUPS-related reports. This difference was not statistically significant, however.

A graphical presentation of the reporting rate of MUPS related ADRs shows an initial rise, followed by a decline to the previous reporting rate of capsules. The Dutch Health Care Insurance Board (GIP) reported that the number of Defined Daily Doses of omeprazole (both capsules and MUPS) dispensed per quarter per 1000 insured persons did not change substantially at the time of the switch from capsules to MUPS. For this reason, changes in prescription data could not explain the changes in the incidence of omeprazole-related reports.

The marketing of a new drug usually involves a slow release onto the market, which causes a slow rise in ADR reports. According to Weber, the total number of ADR reports increases until two years after the introduction and declines thereafter[6]. The sharp rise of the reports we observed may be due to the forced introduction of the new formulation. Moreover, the reporting bias in a spontaneous reporting system varies with the public's and healthcare worker's awareness of ADRs. The media attention to the forced switch evoked a substantially higher awareness of MUPS-related adverse events. Finally, switches to a similar drug with a different pharmaceutical formulation, colour, package or even manufacturer are known to influence ADR reports[8]. Such effects are temporary in most cases.

In our analyses, several statistically significant differences between the frequency distributions over the SOCs became apparent between capsules and MUPS. The differences in distribution among the different SOCs may be explained by several factors. First of all,

pharmacodynamic or safety characteristics between both formulations cannot be excluded.

Overall, the sharp rise in reporting rate alarmed our pharmacovigilance centre. Analysis strongly suggests the presence of a Weber effect due to the forced introduction, as well as some differences in safety profiles. Pharmacovigilance centres should keep in mind that a forced switch to another formulation introduces a temporary rise in the ADR reporting rate of the newer formulation, which does not necessarily imply an alarming signal. Health care professionals should also be aware of this tension, but should not feel restrained from reporting suspected ADRs on new drugs.

References

1 College voor zorgverzekeringen. Farmacotherapeutisch Kompas 2000/2001. Utrecht, The Netherlands: Roto Smeets 2000.

2 Nefarma. Repertorium 1998/1999. The Hague, The Netherlands: SDU Service-centrum Uitgeverijen 1998.

3 Katelaris PH, Phelps G. A randomised controlled comparison of omeprazole capsules and multiple unit pellet system tablets for healing ulcerative oesophagitis. Aust Gastroenterology Week 1999; 14: A113 (Suppl) (Abstract).

4 Anderberg EK. Bioequivalence between omeprazole MUPS® tablets and omeprazole capsules. Gastroenterology 1998; 114(4): A56 (Abstract).

5 Broekmans AW, Lekkerkerker JFF, Koning de GHP, Vree PH. Nieuwe regels voor het melden van bijwerkingen in Nederland na 1995. [New rules for the reporting of adverse drug reactions in the Netherlands.] Ned Tijdschr Geneeskd 1996; 140(22); 1166–7.

6 Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. In: Advances in Inflammation Research, Volume 6. New York: Raven Press, 1984.

7 Anonymous. WHO Adverse Reaction Dictionary. Uppsala, Sweden: WHO Collaborating Centre for International Drug Monitoring, 1995.

8 De Craen AJM, Roos PJ, De Vries AL, Kleijnen J. Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. BMJ 1996; 313: 1624–6.