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► To cite this version:

Hélène Théophile, Ghada Miremont-Salamé, Philip Robinson, Nicholas Moore, Bernard Bégaud, et al.. Relevance of a "Dear Doctor letter" to alert healthcare providers to new recommendations for vitamin D administration. *European Journal of Clinical Pharmacology*, 2011, 67 (7), pp.681-686. 10.1007/s00228-011-1055-y . hal-00699214

HAL Id: hal-00699214

<https://hal.science/hal-00699214>

Submitted on 20 May 2012

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Title: Relevance of a “Dear Doctor letter” to inform about recommendations for vitamin D administration

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Key words: communication/ evaluation studies as topic/ vitamin D/administration, oral/ safety warning / pharmacovigilance.

Word count of the main text: 2101

ABSTRACT

Purpose: After reports of malaise in infants immediately after the oral administration of two brands of vitamin D solutions, recommendations for administration were sent *via* a “Dear Doctor letter” (DDL) to all French paediatricians, pharmacies and some general practitioners (GPs). The DDL and a press release were published on the French Medicines Agency website and sent *via* a mailing list. The present objective was to assess the effectiveness of such a DDL and to gather the opinions of health professionals about the best way to inform them.

Methods: A questionnaire was sent to a national random sample of 145 paediatricians, 680 GPs and 230 pharmacists.

Results: Only 49% of responding paediatricians, 48% of GPs, and 67% of pharmacists were aware of the warning. Among the participating health professionals aware of the warning and who prescribed/dispensed these vitamins, 50% of paediatricians, 68% of GPs declared to have changed their prescription and 68% of pharmacists declared to have modified their advice when dispensing. For the responding health professionals, postal letters remained however the best way to issue safety warnings. Some of them suggested a better identification of the DDL and a wider dissemination of the information to other stakeholders involved in the health system.

Conclusions: Health professionals paid little attention to the DDL that was therefore unlikely to change their practices. A relevant measure to disseminate recommendations for medicine administration could consist in applying stickers on medicine boxes, as it presents the advantage to directly inform the concerned population, *i.e.* the parents.

INTRODUCTION

The occurrence of an adverse drug reaction is, in most cases, due to the nature of the active ingredient(s) and/or to the characteristics of the patient. In some cases however, neither the medicine itself nor the patient are actually at cause, but rather the pattern of administration. In 2006, spontaneous reports to the French pharmacovigilance system of malaise in neonates and infants arose a safety concern related to an incorrect method of medicine administration and to a pipette not adapted for neonates. These malaises occurred immediately after the administration of two brands of an oral solution of vitamin D, the first alone and the second in combination with vitamins A, E and C. A too rapid administration directly to the oropharynx was likely to be the cause of these vagal malaises. As commonly used in Europe and elsewhere to inform on medicine risk [1, 2], the manufacturer concerned, at the request of the French medicines agency (*Afssaps* for *Agence Française de Sécurité Sanitaire des Produits de Santé*), sent a “Dear Doctor Letter” (DDL), to all French paediatricians (n=5,290), pharmacies (n=22,610), and to some general practitioners (GPs) thought to have a predominant paediatric activity (n=553, *i.e.* 0.9% of the 62,994 GPs). Its purpose was to issue recommendations for use and to inform that a new pipette aimed to reduce this risk would shortly be made available [3]. The *Afssaps* published a press release, as usually done in such a case, on its website on October 19, 2006 [4]. It was relayed by the French medical press agency for dissemination in the media. An e-mail with a link to the press release and the DDL was also sent to the subscribers of the *Afssaps* mailing list, to which anyone may freely subscribe.

As the number of DDLs issued over time has increased [5-7] (Fig. 1) in a context of a diversification and sophistication of communication methods, we wished to assess the effectiveness of this strategy and to gather the opinions of physicians and pharmacists on the most adequate methods to convey such information.

METHODS

Study design

A cross-sectional survey was conducted among a national random sample of 145 paediatricians (poll rate: 1/36), 680 general practitioners (poll rate: 1/93) and 230 pharmacies (poll rate: 1/98) in community settings. The random sample of health professionals was obtained from listings of professional bodies with a stratification by administrative region: private practice paediatricians, private practice general practitioners and holders of community pharmacies.

Data collection

Physicians and pharmacists were asked to fill-out a postal questionnaire in order to evaluate if they were aware of and followed new recommendations for the administration of the vitamin formulations concerned. The following questions were asked: 1) *Are you aware of the new recommendations for administration?* 2) *Have you changed your prescription (for paediatricians and GPs)/dispensation (for pharmacists) patterns?* 3) *Do you (for paediatricians and GPs) prescribe these vitamin brands?* 4) *What is your opinion regarding the most effective ways to issue a drug safety warning?* For the latter, we chose to use an open-ended question so as to not influence their replies. To minimize a possible selection bias, we chose to use anonymous pre-paid envelopes for the return of the questionnaires in order to make health professionals feel free to fill out the questionnaire and to limit the possibility of spurious replies.

Analysis

Data were analyzed using STATA[®] software (STATA Corporation, version 8.2 for Macintosh, USA).

RESULTS

The response rates for paediatricians, GPs and pharmacists were 31% (n=45), 37% (n=255) and 40% (n=92) respectively.

Knowledge of the new information and change of practice

Paediatricians

Of the 45 responding paediatricians, 49% (22/45) knew the recommendations and 67% (30/45) prescribed the vitamin brands concerned (Table I). Among the 16 paediatricians who were both informed and prescribed these vitamins, 50% (8/16) stated to have changed their prescription patterns or advices to families and 50% (8/16) not to have modified their explanations when prescribing.

General practitioners

Of the 255 responding GPs, 48% (122/255) knew the recommendations and 50% (127/255) prescribed the vitamin brands concerned (Table I). Among the 68 GPs who were both informed and prescribed these vitamins, 68% (46/68) declared to have changed their prescription patterns or advices to families, 29% (20/68) not to have modified their explanations when prescribing (2 issued explanations on the administration of the vitamins similar to that contained in the DDL, before the alert) and 3% (2/68) did not know whether they had modified or not their explanations.

Pharmacists

Among the 92 responding pharmacists, 67% (62/92) knew the recommendations (Table I). Of these, 68% (42/62) declared to have changed their advice when dispensing, 18% (11/62) not to have modified their explanations and 14% (9/62) not to have sold the vitamin brands concerned since the recommendations were issued.

The percentages of health professionals concerned by the recommendations and who changed their behaviours were 50% for paediatricians, and 68% for both GPs and pharmacists.

Table I: Responses of paediatricians, GPs and pharmacists concerning the issue of safety information about recommendations for vitamin D administration

	Pediatricians	GPs	Pharmacists
	n=45	n=255	n=92
	No (%)	No (%)	No (%)
Knowledge of the new recommendations	22 (49)	122 (48)	62 (67)
Prescriber of the vitamin brands	30 (67)	127 (50)	-
Prescriber and informed	16 (35)	68 (27)	-
Behaviour modification	8 (18)	46 (18)	42 (46)

Opinion regarding the most effective ways to issue a drug safety warning

According to the participating paediatricians, GPs and pharmacists, a postal letter remains the best way to disseminate a safety warning (42%), followed by e-mail/Internet (25%).

Several proposals emerged from their replies that could improve the issue of drug safety warnings: special envelope (*e.g.* yellow envelope) for all DDLs; specific pictogram on all envelopes and letters for safety warnings; alert information in prescription or dispensing software updates; warning stickers on medicine boxes; involvement in issuing of new recommendations of other major stakeholders in the health system such as professional associations, pharmacovigilance centres and, for pharmacists, wholesale distributors.

DISCUSSION

The present study confirms that the current strategy commonly used in Europe, which consists of sending a DDL to health professionals and disseminating the information through an Agency website, is not *a priori* sufficient to satisfactorily change prescription/dispensation patterns. A similarly poor impact of communication strategies has previously been reported [8-14] but this study goes further than previous ones by illustrating the limited capacity of such a strategy to inform health professionals. The difficulty in the present case was to disseminate a safety warning concerning medicines systematically prescribed to all infants and young children but also available without prescription and more often perceived as vitamin supplements than as medicines by the public. Indeed, the safety warning was sent to all paediatricians and pharmacists, but only 49 to 67% of them declared being aware of the alert. Surprisingly, GPs were aware of the alert to the same extent as the other health professionals despite the DDL having been sent only to a minority of them (less than 1%). This finding could suggest that GPs responded that they were aware without really being so, but that would be surprising that GPs gave more inaccurate replies than paediatricians and pharmacists, or else that GPs have been informed by another source than the DDL, which again suggests a poor effectiveness of the DDL. Another relevant result is the relatively high proportion of health professionals who knew the recommendations for administration but did not change their behaviour (30 to 50%). Some of them explained that they did not believe necessary to do this, as a new pipette would soon be available (data not shown). This highlights the difficulty to make a message understood when many ideas coexist and argues for a critical review and analysis of the DDLs by a panel of the intended recipients and by psychologists [15]. However, despite the limited effectiveness of the DDL to convey information, postal letter remained for the responding health professionals the best way to issue a safety warning. Some responders suggested that a better identification of the DDL with, for example, a specific envelope and/or pictogram could improve its influence.

A greater dissemination of the DDL by using postal letter combined with other means of communication could be of great benefit by reaching more people [16-18]. In the present study, some health professionals suggested using e-mail, which has the advantage of issuing the information immediately to a large population [19]. This way of communication already available through the French Medicines Agency website and used by around 20,000 subscribers, should be publicized to maximize the number of subscribers to this mailing list. The involvement of other health professionals such as pharmacy wholesalers, professional medical associations or pharmacovigilance centres, who would then hand the DDL over to the concerned health professionals, could also be worthwhile by increasing the dissemination of the DDL [20, 21]. The wholesalers, in particular, by

distributing the DDL along with medicines, could significantly improve the issuing of a warning, which is now recommended in the 2008 issue of the Volume 9A of pharmacovigilance guidelines in Europe [20]. Improving communication with pharmacists is essential in such campaigns [8, 22-25], as they are the last in the chain to deliver information and have an overall view of the patients' treatment, including self-medication.

However, in the present case, which concerns recommendations for administration of paediatric medicines available without prescription, a measure easy to implement, that could be highly effective, is the application of stickers on medicine boxes. This means of communication, in accordance with the proposals of the European Medicines Agency [26], presents the indisputable advantage to deliver the information at the time when pharmacists need it and to promote an active discussion between the pharmacist and the patient. Besides, at the difference of the other measures proposed, this one presents the advantage to directly reach the concerned population [27, 28], *i.e.*, for the current case, neither the physicians nor the pharmacists, but the parents. Another way to issue the recommendations directly to the parents could have been to launch a general information campaign on liquid administration to babies through specialized magazines.

Limitations

For confidentiality reasons and in accordance to the French law on data protection [29], the manufacturer concerned did not provide us with the addresses used for mailing the DDL. This could have jeopardized the study results if the questionnaire had been sent to health professionals not targeted for the DDL mailing. Actually, this questionnaire was sent to health professionals currently registered to their professional bodies, *i.e.*, professionally active, that was the target population for conveying information about the new recommendations for vitamin D administration.

The participation rates for paediatricians (31%), GPs (37%) and pharmacists (40%) could be qualified of low; however, they are concordant with those found in other published studies using neither follow-up nor fee [30, 31]. Nevertheless, the number of participating paediatricians and pharmacists being limited, generalization of the poor effectiveness of the DDL to the whole source population could be questioned. However, the finding that usefulness of the DDL was poor both for paediatricians and pharmacists gives more confidence in the results. Furthermore, the finding that the GPs knew the new recommendations about vitamin D administration to the same order of magnitude as paediatricians and pharmacists, while few GPs were targeted for the DDL mailing, reinforces the conclusion regarding the limited effectiveness of such a warning.

Finally, the rate of health professionals replying that they were aware of the recommendations for vitamin D administration and thus changed their behaviour has more chance, if biased, to be over- rather than underestimated. Indeed, those who had paid attention to the DDL were probably more prone to spend time to fill out a questionnaire about drug safety. Moreover, this possible overrepresentation in the study sample of health professionals having paid attention to their postal mail could have inflated the proportion of those giving preference for being informed by postal letter. However, it is unlikely that this could alter the proportion of health professionals favouring information through e-mail/Internet since the question referring to the most effective ways to convey a drug safety warning was open-ended.

Conclusions: This study suggested that health professionals paid little attention to the DDL that is therefore unlikely to markedly change practices. Improvements could be made by a better identification of the DDL using a special envelope and a specific pictogram and by a widening dissemination of the information to other stakeholders involved in the health system. In the present case, a relevant measure to disseminate recommendations for drug administration could consist in applying stickers on medicine boxes, as it presents the major advantage to directly inform the concerned population, *i.e.* the parents.

Acknowledgements

We thank the physician and pharmacist professional bodies that performed the random selection, as well as all those who participated to this study.

Funding: None

Competing interests: None

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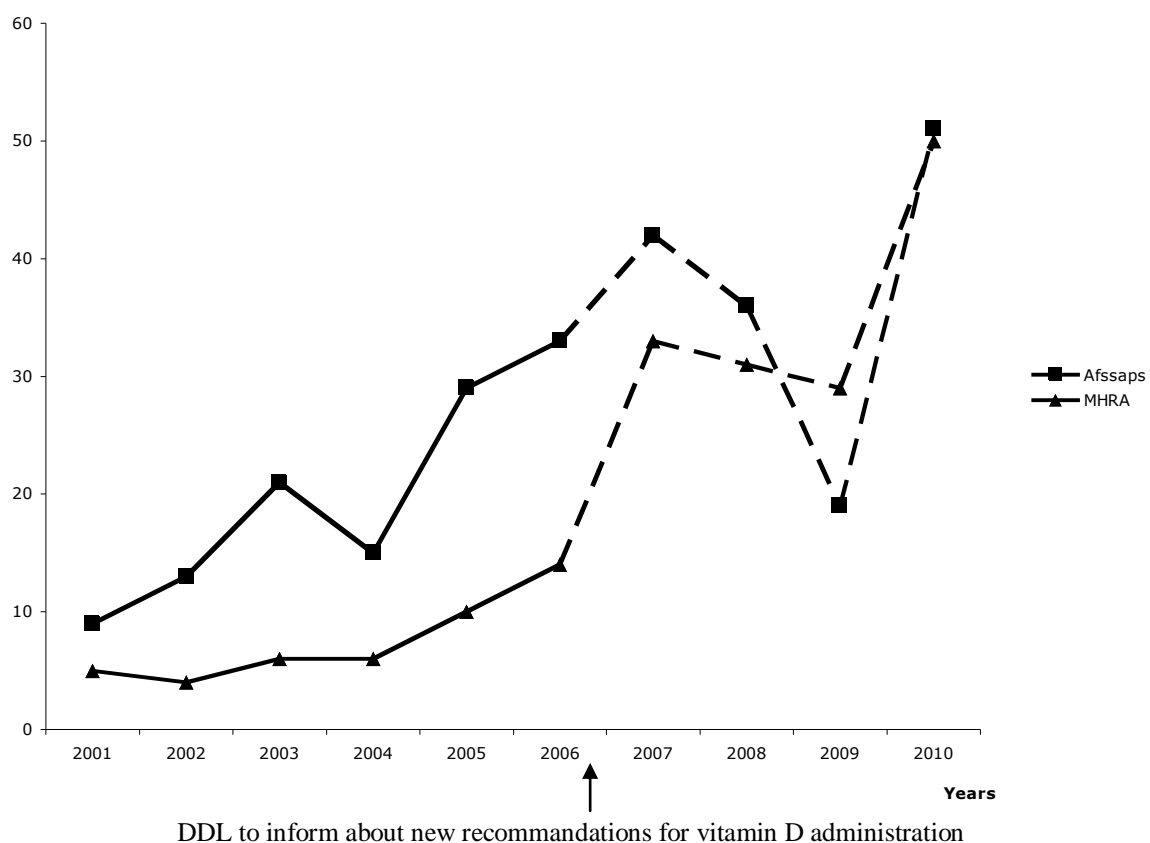


Fig. 1 Temporal trends of the number of DDLs sent to health professionals for safety warnings from 2001 to 2010 in the United Kingdom (Medicines and Healthcare products Regulatory Agency, MHRA) [6] and France (French Medicines agency, Afssaps) [7]. The periods before (continuous line) and after (discontinuous line) the sending of the DDL are indicated.