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Manufacturer's information insert and subjective theophylline side-effects

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ABSTRACT: In Western Europe medicine packages contain an insert prepared by the manufacturer which enumerates the drug side-effects. We investigated the influence of this insert on alleged theophylline side-effects. Forty literate adult asthmatics were randomly allocated into two groups (n=20 each): theophylline packages contained the manufacturer's insert in group A but not in group B. Theophylline was prescribed (10 mg·kg^{-1} body weight *qd*) for one week. During this period the patients filled a diary grading 13 different symptoms from 0 to 3; 5 of these symptoms were listed on the insert as theophylline side-effects. On the eighth day the patients were interviewed and theophylline blood levels measured. Theophylline side-effects were significantly more marked in group A than in group B, whereas the other symptoms were of similar magnitude. Eight patients prematurely stopped their treatment in group A *vs* 3 in group B, because of alleged intolerance. Theophylline blood levels did not differ significantly in the two groups; neither did they in the subgroup which stopped treatment and in the one which complied to prescription. We conclude that side-effects were suggested to the patients by the insert and/or that the insert increased their awareness of side-effects, with a subsequent detrimental influence upon compliance to therapy.

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In Western Europe medicine packages contain an insert prepared by the manufacturer which enumerates the drug side-effects. The purpose of this insert is somewhat obscure. Warning patients against side-effects is probably intended as a sort of liability disclaim by the drug manufacturers. Moreover, one may hope: 1) that patients would be reassured, should they experience one or more of the listed side-effects, since such side-effects would be expected; and 2) that patients' awareness would increase so that they would report any side-effect to their physician and/or stop their treatment to avoid further intoxication.

On the other hand, one may fear that patients, who experience benign side-effects which they would otherwise have ignored, could be disproportionately alarmed when learning from the insert that their symptoms were due to drug intake; even worse, side-effects could be suggested to them by the insert. In both situations the insert could influence compliance to therapy.

Several studies have assessed the influence of written information for patients upon their perception of side-effects and compliance to therapy, with conflicting results [1–3]. In all of these studies, however, the information material was specially devised by the investigators. These special-purpose inserts are not fully comparable, either in their contents (usually they were more detailed) or in their presentation, to the inserts prepared by the drug manufacturers. Surprisingly, the possible influence of these common inserts appears not to have been investigated. We therefore studied the influence of manufacturer's information insert on alleged theophylline side-effects, because theophylline, a drug with known side-effects [4], is often used for the long-term treatment of asthma, a chronic disease with poor compliance to therapy [5].

Methods

Forty literate adult asthmatics entered the study (30 males; mean (SD) age 43 (16) yrs). They were staying in a nursing home for respiratory patients in Briançon (French Alps). The patients were prescribed slow-release theophylline (Dilatrane®, 10 mg·kg^{-1} body weight, half the dosing at 8 am, the other half at 8 pm) for an 8 day treatment period. The medicine was handed to them in the original manufacturer's package. The patients had not been treated by Dilatrane® beforehand. They were allowed to use a metered dose inhaler of β_2-adrenergic-agonist when they felt the need for additional bronchodilation.

The patients were instructed to keep a diary about their symptoms "in order to assess their health state"; the purpose of the study was not revealed to them. Symptoms, appearing in random order in the diary, were: theophylline side-effects listed in the manufacturer's information insert (nausea, insomnia, headache, palpitations, stomach ache), (fig. 1), respiratory symptoms (cough and dyspnoea), and non-respiratory symptoms unrelated to theophylline therapy (dry mouth, joint pains, itching, tiredness, shivering, disturbed smell). Each symptom was scored as follows: 0 = no symptom; 1 = mild; 2 = moderate; 3 = severe. Use of the β_2-agonist was noted.

Effets Indésirables

La théophylline peut parfois entraîner une irritation gastrique (douleurs, nausées), des maux de tête, de l'insomnie, des palpitations, dans ce cas, consultez votre médecin.

Fig. 1. – Photograph of the part of Dilatrane® (slow-release theophylline) manufacturer's insert devoted to side-effects (EFFETS INDÉSIRABLES). Translated from French it reads: Theophylline can sometimes cause gastric irritation (aches, nauseas), headaches, insomnia, palpitations, in that case, consult your physician.

Patients were randomly allocated into two groups (n=20 each): Dilatrane® packages in group A contained the manufacturer's insert, whereas in group B they did not. The prescribing physician was unaware of the presence or absence of the insert. On the eighth day the patients were interviewed by the physician; they were asked if they had taken their treatment as prescribed, theophylline blood levels were measured (6 h after morning intake), the diaries collected and the remaining pills counted to check compliance to therapy. The patients were then asked by another observer whether or not their Dilatrane® package contained an insert and, if yes, whether or not they had read it.

Each symptom was evaluated by dividing the sum of daily scores by the number of days the patient actually took Dilatrane®.

Results

Theophylline side-effects were more marked in group A than in group B: mean (SEM) symptom score per treatment day = 0.74 (0.13) and 0.28 (0.07), respectively ($p<0.005$ with Student's t-test and $p<0.05$ with the non-parametric U test of Mann-Whitney). The other symptoms did not differ significantly: 0.35 (0.11) *vs* 0.35 (0.13). Eight group A patients prematurely (on average after 1.4 day) stopped their treatment because of alleged intolerance, whereas only 3 group B patients ($0.05<p<0.1$ with Chi squared test) did so (after 2.6 days).

In the subgroup of patients who prematurely stopped their treatment, theophylline blood levels could be measured within 10 h after the last intake for 8 patients (6 from group A) who told a staff member that they did not want to continue Dilatrane® therapy because of intolerance. They were not measured for 3 patients (2 from group A) because non-compliance was disclosed only on the eighth day interview, when therapy had been interrupted for several days. Theophylline blood levels did not differ significantly in group A and B: mean value (SEM) = 7.6 (0.7) and 7.8 (0.8) $\mu g \cdot ml^{-1}$, respectively; neither did they in the subgroup of patients who prematurely stopped therapy (n=8) and the subgroup (n=29) which complied to prescription: 9.2 (1.4) and 7.3 (0.5) $\mu g \cdot ml^{-1}$, respectively.

Use of the β_2-agonist aerosol was similar in the two groups. All but one group A patient claimed to have read the insert.

Discussion

We elected to study asthmatics staying in a nursing home because such patients usually get their medicines handed to them by a staff member for a period of several days. In France it is fairly common for asthmatics to spend a few weeks in such health facilities located at high altitude, where the atmosphere is supposedly favourable for their asthma. We thus believe that the patients studied were no different from regular asthmatics.

Although a diary was necessary to prospectively evaluate theophylline side-effects, it may have increased patients alertness to their symptoms. For obvious reasons our interest in assessing theophylline side-effects had to remain concealed to the patients. Thus, the purpose of the study was not disclosed to them, and theophylline side-effects were interspersed among other symptoms in the diary. It is likely that our patients did not suffer initially from the listed non-respiratory symptoms. The diary may thus have raised a negative feeling: the fear of suffering from "new" symptoms, perhaps as a consequence of therapy. To counterbalance this, we included familiar respiratory symptoms that asthmatic patients would expect to be improved with therapy. Despite these precautions, overestimation of symptoms remains a possibility.

However, the two groups differed significantly only for theophylline side-effects, the insert being responsible for the difference. We cannot exclude the possibility that patients from the two groups talked to each other about the diaries and exchanged inserts, but this would tend to attenuate the difference between the two groups rather than to create it. In addition, no more than two or three patients participated in the study for a given week among the 60 or so patients who were present in

the nursing home at that time. We are fairly confident that the study, which ran over a six month period, went unnoticed.

When the insert was available, nearly all patients read it, confirming that information material is read by a high percentage of patients [1]. In the group which had access to the manufacturer's information insert, patients complained significantly more of theophylline side-effects. It is thus likely that side-effects were suggested to them by the insert and/or that the insert awoke their awareness of side-effects.

One purpose of warning patients against drug side-effects is to stop a treatment that might be toxic. Here, theophylline blood levels of patients who prematurely stopped treatment were in the non-toxic range [4] and similar to that of patients who complied to prescription; thus the decision to stop therapy appears to be unjustified. The reason for non-compliance was alleged side-effects. Since compliance to therapy is low in asthma [5], as in other chronic diseases [6], it is important to identify factors which influence it. Our data suggest that the manufacturer's information insert is one of them. We could examine the insert found in slow-release theophylline packages from the same manufacturer in Belgium, Italy, The Netherlands, United Kingdom and West Germany: all contained a paragraph about side- effects fairly similar to that of the French insert. Asthmatics may, thus, use theophylline inadequately in these countries too.

Previous studies on the influence of written information upon compliance to therapy yielded conflicting results [1–3]. For example, compliance tended to improve in patients taking penicillin but tended to decrease in those taking non-steroidal anti-inflammatory agents [7]. This suggests that the overall influence of inserts could depend on the drug, the disease, the patients and, perhaps, other untested factors such as treatment duration. The way the information is presented to patients is probably also important. For example, mentioning the percentage of occurrence of side-effects may not have the same influence as merely listing them.

The general public show eagerness for more information about medicines, which is legitimate. However, as our study suggests, informing patients about possible side-effects might result in non-compliance. Improving patient education about proper drug use is one solution to this dilemma. Education is a far more complex process than information and could be defined as giving both the information and the means to handle it. Recommendations for more detailed information inserts have been issued [8] but their role in patient education has not been assessed. In the USA the issue of written information for patients was much debated in the early eighties, but the Food and Drug Administration Patient Package Insert Program was stopped, apparently for economic reasons [9], before firm conclusions were reached. Further studies are certainly needed in order to design better inserts, but it is doubtful that patient education could be achieved using written information exclusively [10].

We suggest that physicians should give verbal explanations to their patients about slow-release theophylline pharmacology and about the insert.

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Encart d'information des producteurs et effets latéraux subjectifs de la théophylline. D. Vesco, M. Toumi, F. Faraj, H. Razzouk, J. Orehek.

RÉSUMÉ: En Europe de l'Ouest, les emballages de médicaments comportent un encart préparé par le fabricant, qui énumère les effets secondaires des médicaments. Nous avons investigé l'influence de cet encart sur les effets latéraux signalés par les patients. Quarante asthmatiques adultes sachant lire ont été alloués au hasard en 2 groupes de 20: les emballages de théophylline contenaient l'encart du fabricant dans le groupe A, mais pas de le groupe B. La théophylline a été prescrite à raison de 10mg·kg^{-1} de poids et par jour pendant une semaine. Pendant cette période, les patients ont rempli un carnet-calendrier graduant 13 symptômes différents de 0 à 3; 5 de ces symptômes étaient repris dans l'encart sur les effets latéraux de la théophylline. Les patients ont été interviewés le 8e jour et leur taux sanguin de théophylline a été mesuré. Les effets secondaires de la théophylline étaient significativement plus marqués dans le groupe A que dans le groupe B, alors que les autres symptômes étaient d'importance similaire. Huit patients ont interrompu prématurément leur traitement dans le groupe A, contre trois dans le groupe B, en

raison d'une prétendue intolérance. Les taux sanguins de théophylline ne différaient pas de façon significative dans les deux groupes, ni dans le sous-groupe qui a interrompu le traitement par rapport à celui qui a suivi les prescriptions. Nous concluons que les effets secondaires ont été suggérés aux patients par l'encart et/ou que l' encart augmente leur degré de perception des effets secondaires, avec une conséquence défavorable sur l'observance à l'égard du traitement.
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