Postmarketing surveillance study of a non-chlorofluorocarbon inhaler according to the safety assessment of marketed medicines guidelines

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Abstract

Objective To evaluate the safety of a non-chlorofluorocarbon metered dose salbutamol inhaler.
Design This was a postmarketing surveillance study, conducted under formal guidelines for company sponsored safety assessment of marketed medicines (SAMM). A non-randomised, non-interventional, observational design compared patients prescribed metered doses of salbutamol delivered by inhalers using either hydrofluoroalkane or chlorofluorocarbon as the propellant. Follow up was three months.
Setting 646 general practices throughout the United Kingdom.
Subjects 6614 patients with obstructive airways disease (1667 patient years of exposure).
Main outcome measures Proportions of patients who were: admitted to hospital for respiratory diseases, reported adverse side effects, or withdrew because of adverse affects.
Results There were no significant differences between the hydrofluoroalkane (HFA 134a) and chlorofluorocarbon inhaler groups in relation to the proportions of patients admitted to hospital for respiratory diseases (odds ratio 0.75; 95% confidence interval 0.51 to 1.08) or the proportions who reported adverse events (1.01; 0.88 to 1.17). However, more patients using the hydrofluoroalkane inhaler than the chlorofluorocarbon inhaler withdrew because of adverse events (3.8% and 0.9% respectively).
Conclusion The hydrofluoroalkane inhaler was as safe as the chlorofluorocarbon inhaler when judged by hospital admissions and adverse affects. The study design successfully fulfilled the recommendations of the guidelines. Differences between postmarketing surveillance studies and randomised clinical trials in assessing safety were identified. These may lead to difficulties in the design of postmarketing surveillance studies.

Introduction

The need to monitor the safety of new medicines in large populations of patients is well established,[1] particularly since an average of only 1480 patients is recruited into clinical trial programmes before a new drug is marketed.[2] It is only then that a comprehensive assessment of its safety can be made. Formal postmarketing surveillance conducted in broadly based clinical settings contributes to the evaluation of drug safety.[1]

A review of 31 postmarketing surveillance studies (conducted under the voluntary guidelines issued in 1987[3 4]) concluded that these had made only a limited contribution to the assessment of drug safety. The main criticisms were that patients were identified prospectively for inclusion, no comparison groups were used, and recruitment to the studies was slow. Furthermore, results were seldom published, so prescribers remained ignorant of the findings. To address these concerns, formal guidelines for the design of company sponsored safety assessment of marketed medicines were introduced in 1994 (table 1).[1]

We conducted a postmarketing surveillance study of the first licensed, pressurised, metered dose inhaler to use a non-chlorofluorocarbon propellant—the hydrofluoroalkane 134a salbutamol sulphate inhaler (Airomir, 3M). The study complied with the safety assessment of marketed medicines guidelines.[1] Controlled trials had shown that metered dose salbutamol inhalers using hydrofluoroalkane as the propellant were comparable in terms of efficacy and safety to existing salbutamol inhalers using chlorofluorocarbon as the propellant.[5–8] We aimed to evaluate the safety of the hydrofluoroalkane inhaler in patients prescribed salbutamol in primary care by comparing it with an inhaler using chlorofluorocarbon as the propellant.

Methods

An independent steering committee was formed, as recommended by the guidelines. The committee's responsibilities included approving the study design, monitoring progress, and reviewing reports of adverse events.

Study design

An open label, non-randomised, non-interventional observational study design was chosen, with the aim of recruiting rapidly a large cohort of patients representative of the general population being treated with pressurised metered dose salbutamol inhalers. Normal clinical practice was followed. Neither the patient nor the doctor had to undertake any procedures related to

Table 1 Main criticisms of postmarketing surveillance studies and recommendations to address these[1]

Main criticisms	Safety assessment of marketed medicines recommendations
Prospective identification of patients for inclusion in the study	Patients to be enrolled prospectively, but this must not influence the decision to prescribe, that is:
	Drug to be prescribed in usual manner
	Drugs must be prescribed solely for the normal clinical indication
	Patients must be true candidates for the medicine being evaluated
Lack of comparator group makes it difficult to assess causal relation between drug and event	Include appropriate comparator group(s) (with the same disease/indication, receiving the usual care)
Slow recruitment results in inadequate study populations and delay in identifying any hazards	Adherence to a clearly defined study plan so that recruitment is not drawn out, for example:
	Minimal selection criteria, so that study population is representative of the general population of users
	Exclusion criteria limited to contraindications specified in the data sheet/summary of product characteristics
Results of postmarketing surveillance studies are seldom published	All suspected adverse reactions to be reported in the usual way
	Serious adverse reactions to be reported to the Medicines Control Agency within 15 days
	Provision of brief progress report to the Medicines Control Agency every 6 months
	Final report to Medicines Control Agency within 3-6 months of completing follow up
	Study results to be submitted for publication
	Other guidelines for good practice:
	Studies should not be conducted for promotional purposes
	Highest standards of professional conduct and confidentiality must be maintained

the study. Patients did not have to make additional visits to the surgery. Recruitment of patients, therefore, reflected the general prescribing habits for salbutamol in relation to all the indications for which the drug had been licensed.

General practitioners

Altogether, 11 300 general practitioners throughout the United Kingdom were invited to participate. The letter of invitation described the rationale for replacing chlorofluorocarbon in metered dose inhalers, the design and objectives of the study, the predicted workload, the payment schedule, and the number of patients to be enrolled.

Patients

To generate a large population, patients were recruited in the ratio of one using a chlorofluorocarbon inhaler to five using a hydrofluoroalkane inhaler. They were considered for treatment with the hydrofluoroalkane inhaler only after the clinical decision to start or modify salbutamol treatment had been made. The first patient in each block of six continued using their existing chlorofluorocarbon inhaler, while the next five were prescribed the hydrofluoroalkane inhaler.

Data collection

Data were collected by the investigator from the patients' medical records for the three month study period. The quality of data was ensured by conducting source data verification on one randomly selected patient in each group of six patients at each centre.

Statistical methods

The planned sample size of 6468 subjects provided 80% statistical power to detect a relative risk of 2.0 for patients having at least one admission to hospital (for the condition for which salbutamol was prescribed) at a significance level of 5%. The underlying assumption was that the rate of hospital admission during the three months of the study would be not less than 1.25% in the group using chlorofluorocarbon inhalers.

Baseline characteristics relating to the severity of the condition being treated in each group were compared by computing odds ratios and associated 95% confidence intervals. Severity was inferred from the daily dose of inhaled steroids—>800 μg/day beclomethasone dipropionate or >400 μg/day fluticasone propionate was considered to indicate a serious condition. Logistic regression analysis was used to analyse the rates of patient-doctor consultations (that is, hospital admission, attendance at accident and emergency units, unscheduled surgery visits, and unscheduled home visits). The effect of treatment was assessed after adjusting for the following covariates: sex, age, ethnic origin, severity, and duration of condition. The incidence of adverse events in each treatment group was compared using Fisher's exact test. Separate analyses were performed for individual adverse events, serious adverse events, and those probably or possibly related to study treatment.

Consent

The safety assessment of marketed medicines guidelines states that ethics committee approval is not required for a non-randomised, non-interventional study. However, patients did give written informed consent to information being extracted from their notes and used in the study.

Results

Altogether, 1223 general practitioners (10.8%) accepted the invitation to participate and 1096 confirmed their agreement after they had received a detailed description of the study. Six hundred and forty six of these general practitioners, widely distributed throughout the United Kingdom, participated and recruited a total of 6614 patients (5402 of whom were using a hydrofluoroalkane inhaler and 1212 a chlorofluorocarbon inhaler). The two groups were comparable in terms of age, sex, ethnic origin, and diagnosis (table 2). The first patient was enrolled on 21 May 1995 and the study was completed 15 months later.

Table 2 Summary of demographic and baseline data

Variable	Treatment group: Hydrofluoroalkane inhaler (n=5402)	Chlorofluorocarbon inhaler (n=1212)
Mean (SD) age (years)	40.6 (20.8)	42.7 (22.0)
Sex (% (No)):		
Male	46.9 (2534)	47.7 (578)
Female	53.1 (2865)	52.3 (633)
Ethnic origin (% (No)):		
White	94.5 (5102)	94.5 (1145)
Non-white	5.5 (297)	5.5 (67)
Diagnosis (% (no)):		
Asthma	88.1 (4758)	87.2 (1057)
Chronic obstructive pulmonary disease	4.8 (257)	5.0 (61)
Asthma and chronic obstructive pulmonary disease	3.5 (191)	4.1 (50)
Other	3.7 (196)	3.5 (44)

Data for a few patients were unavailable.

Admissions and consultations

There was no appreciable difference between the groups in the rate of hospital admissions attributable to the condition for which salbutamol had been prescribed (hydrofluoroalkane inhaler 2.3% and chlorofluorocarbon inhaler 3.1%; odds ratio 0.75 (0.51 to 1.08)) (table 3). Multivariate analysis—adjusting for age, sex, ethnic origin, disease duration, and severity—showed no statistically significant differences (odds ratio 0.84 (0.58 to 1.23)).There were no appreciable differences between the groups in the proportions of patients who attended accident and emergency departments, made unscheduled visits to the surgery or had home visits (table 3).

Adverse events

General practitioners recorded adverse events in similar proportions of patients in each group (24.8% hydrofluoroalkane inhalers and 24.5% chlorofluorocarbon inhalers; odds ratio 1.01 (0.88 to 1.17)) (table 4). The most commonly reported adverse affects were infection, bronchospasm, and upper respiratory tract infection. General practitioners attributed more adverse events to hydrofluoroalkane inhalers (3.1%) than to chlorofluorocarbon inhalers (0.7%). No deaths were attributable to the condition for which salbutamol had been prescribed or to the study medications. The incidence of serious adverse events was higher in patients using chlorofluorocarbon inhalers (3.7%) than in those using hydrofluoroalkane inhalers (2.7%) (table 4).

Withdrawal from the study

Overall, more patients using the hydrofluoroalkane inhaler withdrew from the study. ($P<0.001$) (table 5). Most patients in both groups (10.4% hydrofluoroalkane inhaler and 3.1% chlorofluorocarbon inhaler) withdrew for reasons unrelated to safety. These included intercurrent illness, lost to follow up, and inadvertent prescription errors. In the hydrofluoroalkane salbutamol group, 3.1% patients withdrew because they disliked the taste. More patients using the hydrofluoroalkane inhaler stopped taking study medication because of adverse events (3.8% compared with 0.2% in the chlorofluorocarbon inhaler group). The proportion of patients who stopped using the hydrofluoroalkane inhaler because of adverse events fell from 1.9% during the first 30 days to 0.7% between days 61 and 90. Over 80% of patients in both groups completed three months of treatment with the study medication.

Discussion

We describe a non-interventional, non-randomised observational study undertaken to document early postmarketing experience with a metered dose salbutamol aerosol inhaler using hydrofluoroalkane as the propellant. The study is unusual in that it evaluated the reformulation of an existing drug in a new propellant system. It aimed to evaluate the safety of a hydrofluoroalkane inhaler by comparing it with existing chlorofluorocarbon inhalers in patients prescribed salbutamol in primary care. We believe that this is the first postmarketing surveillance study conducted under safety assessment of marketed medicines guidelines to be submitted for publication.

The study met the objectives of the safety assessment of marketed medicines guidelines and also fulfilled standards laid down in the European Agency for the Evaluation of Medicinal Products' guidelines for

Table 3 Percentage (number) of patients with at least one unscheduled medical contact, with odds ratios

	% (No) in treatment group: Hydrofluoroalkane inhaler	Chlorofluorocarbon inhaler	Odds ratio (95% CI): Univariate model	Multivariate model*
Hospital admissions	2.3 (124)	3.1 (37)	0.75 (0.51 to 1.08)	0.84 (0.58 to 1.23)
Visits to accident and emergency departments	1.3 (68)	1.6 (19)	0.80 (0.48 to 1.34)	0.78 (0.47 to 1.31)
Unscheduled surgery visits	31.9 (1724)	32.7 (396)	0.97 (0.85 to 1.10)	1.01 (0.88 to 1.16)
Unscheduled home visits	4.8 (261)	5.2 (63)	0.93 (0.70 to 1.23)	1.05 (0.79 to 1.40)

*Adjusted for effects of sex, age, ethnic origin, duration, and severity of disease.

Table 4 Percentage (number) of patients who had at least one adverse event, with odds ratios

Adverse events	Treatment group (% (No)): Hydrofluoroalkane inhaler (n=5402)	Chlorofluorocarbon inhaler (n=1212)	Odds ratio (95% CI)
Most common adverse events:			
Infection	4.5 (245)	5.6 (68)	
Bronchospasm	2.2 (121)	3.0 (36)	
Upper respiratory tract infection	2.0 (109)	2.6 (31)	
≥1 adverse event	24.8 (1338)	24.5 (297)	1.01 (0.88 to 1.17)
≥1 adverse effect considered to be related to study treatment	3.1 (170)	0.7 (9)	4.34 (2.22 to 8.52)
≥1 serious adverse event	2.7 (145)	3.7 (45)	0.72 (0.51 to 1.01)

postmarketing surveillance studies on non-chlorofluorocarbon metered dose inhalers, which came into effect while the study was in progress (table 6).[9] The use of these guidelines in this and future trials is expected to increase the credibility of postmarketing surveillance studies.

The response rate of general practitioners to the invitation to participate in the study was high (10.8%). Conventional wisdom regarding large mailshots suggests that a response rate between 5% and 8% is usual.

The study highlighted several differences in study design or conduct and outcome between a postmarketing surveillance and randomised controlled trials. To ensure broad comparability between the groups, control patients were recruited at the same time from the same general practices as the patients using the hydrofluoroalkane inhalers. Nonetheless, because of the open nature of the study, it was anticipated that there would be differences between groups in, for example, adverse events attributable to treatment. We used the number of patients who had been admitted to hospital at least once for the condition for which salbutamol had been prescribed as the primary outcome variable. This provided an objective indication of a severe exacerbation, likely to be documented fully in the patient's general practitioner records and to be less influenced by subjective perceptions of the effects of new medication. Other objective measures of asthma control are available, but incorporating these into the study would have meant imposing standardisation of treatment upon general practitioners, which is contrary to the safety assessment of marketed medicines guidelines. The pattern of similar hospital admission rates, other unscheduled medical consultations, and adverse event reports indicates that the safety profile of hydrofluoroalkane salbutamol inhaler is similar to that of chlorofluorocarbon salbutamol inhaler.

In randomised clinical trials both the prescriber and patient are often blinded to the medication, but this is clearly not usual in clinical practice. The ability to assess the use of medicines under normal clinical conditions would have been lost had the study been blinded.

The non-interventional design allowed patients who were already using a chlorofluorocarbon salbutamol inhaler to continue this. These patients therefore represented a "survivor population" who were able to tolerate continued treatment, as those unable to tolerate the chlorofluorocarbon salbutamol inhaler would have stopped taking it before the recruitment visit. This factor was identified by the steering committee during the design stage as being likely to result in a higher incidence of adverse events being attributed to the hydrofluoroalkane inhaler because of the change of medication in this group. In interpreting these results, it is the size of this and other related effects—as measured by odds ratios and confidence intervals, rather than just their statistical significance—that is of primary importance. The survivor bias might have been overcome by switching all the patients in the chlorofluorocarbon inhaler group to a single new chlorofluorocarbon salbutamol product. However, this option is not available within the confines of a non-interventional study. Survivor bias is likely to occur in all studies using this design and cannot be eliminated.

The proportion of patients reporting adverse events was similar in both groups, although we confirmed the anticipated phenomenon that more events would be attributed to the new formulation. The events most often considered by general practitioners to be related to the hydrofluoroalkane salbutamol formulation were those commonly associated with salbutamol treatment—headache, nausea, and tremor. This is unlikely to be the result of an increased availability of salbutamol since clinical studies have shown that the adverse event profiles of hydrofluoroalkane inhaler and chlorofluorocarbon salbutamol are the same.[5–8]

The greater attribution of adverse events to the prescription of a new medication was reflected in the higher rate of withdrawals because of adverse events in the hydrofluoroalkane inhaler group. There are a number of reasons for this. Patients are likely to notice

Table 5 Percentage (number) of patients withdrawing from study treatment

Withdrawal	Treatment group: Hydrofluoroalkane inhaler (n=5402)	Chlorofluorocarbon inhaler (n=1212)
Total withdrawals*	17.6 (950)	4.8 (58)
Withdrawals casued by:		
Death	0.3 (15)	0.6 (7)
Adverse event	3.8 (205)	0.9 (11)
Not related to safety	9.0 (602)	3.2 (39)
Taste	3.1 (167)	0.2 (2)
Withdrawals on days 1-30	6.2 (333)	0.7 (9)
Adverse events days 1-30	1.9 (101)	0.2 (2)
Withdrawals on days 61-90	3.9 (211)	1.2 (15)
Adverse events days 61-90	0.7 (36)	0.2 (3)

*P<0.001.

Table 6 Recommendations of guidelines of European Agency for the Evaluation of Medicinal Products[9] that were met by this study

Guidelines category	Features of present study
Study design	Observational cohort is acceptable
	Control group is necessary and will usually be the chlorofluorocarbon product
	Enrolment of a smaller number of patients in the control group than the study group is acceptable
Patient types and numbers	Enrolment of patients currently using chlorofluorocarbon inhaler acceptable
	Sample was sufficient to test the hypothesis
	No patients were concurrently participating in other postmarketing surveillance studies
	Patient inclusion was as close as practicable to the real prescribing situation
Treatment period	The 3 month treatment period fell within the 3-6 month recommended range
Concomitant medications	Patients may continue with concomitant treatments as per the product data sheet
Reporting parameters	These complied with the guidelines' recommendations—that is, basic demography, indication, product under study and concomitant medications, date treatment started and stopped, serious adverse events

Key messages

- Credibility of postmarketing surveillance studies is expected to increase after the introduction of guidelines covering their conduct
- The study design successfully fulfilled the requirements of these guidelines in terms of the number, rate, and geographical spread of patients recruited
- Safety of salbutamol inhalers using hydrofluoroalkane and chlorofluorocarbon as propellants is similar
- Important differences in study design/conduct and outcome between a postmarketing surveillance study and a randomised clinical trial merit further consideration.

a difference in the physical sensation and taste of all reformulated aerosol products, and it is important to educate both doctors and patients during the transition from chlorofluorocarbon propellants to chlorofluorocarbon-free propellants. The lack of educational material in the present study may explain why around 3% patients stopped using the hydrofluoroalkane inhaler because they disliked the taste. The proportion of patients who withdrew fell from 1.9% during the first 30 days to 0.7% in the last 30 days, indicating that with continued treatment patients became used to their new medication. Thus, by the end of follow up, a survivor population for hydrofluoroalkane inhalers was developing in the same way that a survivor population had developed for chlorofluorocarbon inhalers before the study.

Our findings support the experience of clinical trials, showing that the reformulation of salbutamol sulphate in a hydrofluoroalkane propellant system does not result in changes in safety when compared with a chlorofluorocarbon salbutamol formulation. The study design was successful in terms of the number, rate, and geographical spread of patients recruited, and shows that it is possible to fulfil the recommendations of the safety assessment of marketed medicines guidelines. The extent to which postmarketing surveillance studies can ever exclude bias (for example a survivor population) will need further consideration by the safety assessment of marketed medicines' committee.

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Contributors: JGA was chairman of the independent steering committee; CDF, WFH, and DRRW were members of the independent steering committee; JGA and WFH were responsible for clinical input into the design, review and interpretation of data; CDF was responsible for statistical input into the design, review and interpretation of data; DRRW was responsible for epidemiological input into the design, review, and interpretation of data; SMW was responsible for input into the design, review and interpretation of data, as well as for overall study management. JGA will act as guarantor for the paper.

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Conflict of interest: SMW is employed by 3M Health Care. The other authors were members of the steering committee, which met under the auspices of 3M Health Care.

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A memorable patient

An effective reproof

The man in the wheelchair was in his 70s. The ravages of longstanding rheumatoid arthritis had played havoc with his joints. He wanted advice about his dry eyes. One of the students took a careful history and another gave a detailed description of the gross deformity of the patient's hands. I ventured that he must find everyday manual tasks virtually impossible. I examined his eyes and gave him advice about artificial tears and other supplementary measures. The students left for their coffee break.

"Excuse me doctor," the patient said, "I did not want to embarrass you when the students were here. My hands may look awful but they actually work quite well. I would like you to have these." He pushed across the desk a small plastic box in which were a dozen or so trout flies. "I tied them." he said.

The flies have long since been lost in the undergrowth adjoining the local chalk streams. But the two lessons will be with me forever. Firstly, remarkably good function can be maintained in spite of gross disruption of normal anatomy and, secondly, that a reproof is most effective if spoken gently and with courtesy. When the students came back I told all.

Andrew Elkington, *professor of ophthalmology, Southampton*

We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.