Sedation with "non-sedating" antihistamines: four prescription-event monitoring studies in general practice

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Abstract

Objectives To investigate the frequency with which sedation was reported in post-marketing surveillance studies of four second generation antihistamines: loratadine, cetirizine, fexofenadine, and acrivastine.
Design Prescription-event monitoring studies.
Setting Prescriptions were obtained for each cohort in the immediate post-marketing period.
Subjects Event data were obtained for a total of 43 363 patients.
Main outcome measure Reporting of sedation or drowsiness.
Results The odds ratios (adjusted for age and sex) for the incidence of sedation were 0.63 (95% confidence interval 0.36 to 1.11; $P = 0.1$) for fexofenadine; 2.79 (1.69 to 4.58; $P < 0.0001$) for acrivastine, and 3.53 (2.07 to 5.42; $P < 0.0001$) for cetirizine compared with loratadine. No increased risk of accident or injury was evident with any of the four drugs.
Conclusions Although the risk of sedation was low with all four drugs, fexofenadine and loratadine may be more appropriate for people working in safety critical jobs.

Introduction

Antihistamines are often used to treat the symptoms of allergies such as seasonal and perennial allergic rhinitis and urticaria. The first generation antihistamines have been associated with side effects, particularly sedation.[1] Second generation antihistamines are therefore favoured over the first generation drugs, not because of greatly improved efficacy but because they have fewer side effects, especially sedation.[2–4]

Although the second generation antihistamines are known to all have similar efficacy,[3] the extent of their sedative effects is not well established. To further examine the sedative effects of four commonly prescribed antihistamines—loratadine, cetirizine, fexofenadine, and acrivastine—we analysed the results of four non-interventional observational cohort studies of these drugs performed by the Drug Safety Research Unit. These studies correlated prescriptions issued in general practice with events reported by the patients to their general practitioners after the drug was dispensed. By monitoring these events in a substantial population of allergy sufferers, without the restrictions imposed by clinical trials methodology, it was possible to measure differences in side effects between these drugs.

Methods

The methods of prescription-event monitoring have been previously described in detail.[5] In brief, the general practitioner writes a prescription which the patient takes to the pharmacist. The pharmacist sends all these prescriptions to the Prescription Pricing Authority, which under conditions of full confidentiality, provides electronic copies of the exposure data to the Drug Safety Research Unit. After three, six, or 12 months, "green form" questionnaires are sent to the general practitioners who wrote the original prescriptions. These questionnaires seek to determine any event experienced by patients while they were taking the drug and for a period afterwards. General practitioners are also asked to indicate whether the event was considered to be related to the drug, although they are not required to make this connection. Additionally, the prescribers are asked to indicate whether the drug has been stopped and, if so, the reason for this. All reported pregnancies are followed up to determine the outcome and the cause of all deaths are established. Both the exposure (prescription) and the outcome (event) data are computerised for analysis.

Statistical analysis

The number of events observed during the treatment period in each individual patient is recorded and the incidence density for each event is calculated using the equation:

$$ID_t = \frac{\text{No of events during treatment period } t}{\text{No of patient-months of treatment for period } t} \times 1000$$

The incidence density is the measure of the number of reports of each event per thousand patient-months of exposure to the drug. We calculated incidence densities for various time intervals: the first month of exposure (ID_1), during months 2-6 (ID_2), and during all months of treatment (ID_A). The difference between the incidence density in the first month and that in the second to sixth months ($ID_1 - ID_2$) and the 99% confidence interval for this difference were also calculated. Incidence densities were calculated for all of the events reported, to give an indication of which events were reported significantly more frequently in

Table 1 Number (percentage) of patients treated with antihistamines according to age and sex

	Acrivastine (n=7863)	Cetirizine (n=9554)	Fexofenadine (n=16 638)	Loratadine (n=9308)
Age (years):				
<30	3169 (40.3)	4648 (48.6)	5979 (35.9)	4574 (49.1)
30-<60	3036 (38.6)	3353 (35.1)	6453 (38.8)	3256 (35.0)
⩾60	1060 (13.5)	819 (8.6)	2405 (14.5)	678 (7.3)
Not known	598 (7.6)	734 (7.7)	1801 (10.8)	800 (8.6)
Sex:				
Men	2833 (36.0)	3945 (41.3)	6578 (39.5)	3912 (42.0)
Women	4899 (62.3)	5457 (57.1)	9880 (59.4)	5179 (55.6)
Not known	131 (1.7)	152 (1.6)	180 (1.1)	217 (2.3)

the first month of exposure. We calculated non-adjusted and age and sex adjusted odds ratios for drowsiness or sedation for fexofenadine, cetirizine, and acrivastine using loratadine as baseline.

Ethical considerations

Prescription-event monitoring is a form of pharmacovigilance, an exercise which has its legal basis in European Union directives 65/65 and 75/319 and in regulation 2309/93. The method of study (records only research) also complies with the guidelines on the practice of ethics committees in medical research involving human subjects issued by the Royal College of Physicians of London in August 1996.

Results

The data collection periods for the four drugs were May to August 1989 for cetirizine and loratadine, May 1989 to September 1990 for acrivastine, and March to August 1997 for fexofenadine. The response rates (number of green forms returned/number of green form sent) were 50.7% for loratadine, 50.9% for fexofenadine, 56.5% for acrivastine, and 57.4% for cetirizine.

Table 1 gives the age and sex distribution of patients treated with each antihistamine. The demographics of each cohort were roughly similar. A higher proportion of women than men were prescribed antihistamines, and younger people were more likely to receive the drugs than elderly people.

Figure 1 shows the most frequently reported events for loratadine in the first month of treatment and corresponding values for the other antihistamines. The differences between the antihistamines in the incidence density of events classified as "drowsiness or sedation" are further investigated in table 2. The unadjusted and age and sex adjusted odds ratios show that loratadine and fexofenadine are associated with a lower incidence of sedation than acrivastine and cetirizine (table 3). Since sedation may result in an increased risk of other events such as accident and injury, we analysed the incidence density of these events in the first month of treatment (fig 2). There was no increased risk of accident or injury with any of the four drugs.

Discussion

It has been recognised for over 30 years that drug safety depends not only on preclinical studies but also on post-marketing surveillance.[6] Post-marketing prescription-event monitoring studies observe large cohorts and aim to provide data on around 10 000 patients for each drug. The data consist of the real life experiences of patients, who are often taking concomitant drugs for other conditions. To date, 65 prescription-event monitoring studies have been undertaken with a mean cohort size of 11 055 patients.

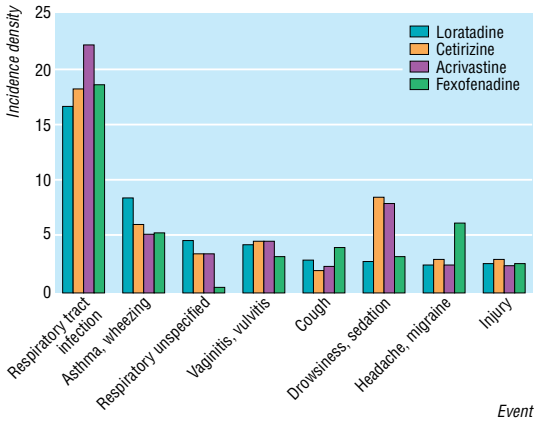

Fig 1 Eight most commonly reported events for loratadine in first month of treatment and corresponding incidence densities for acrivastine, cetirizine, and fexofenadine

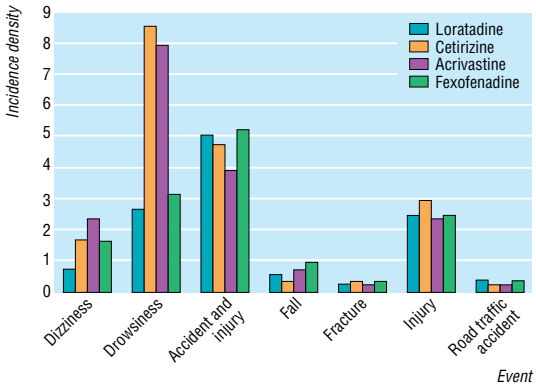

Fig 2 Incidence density of events related to sedation in the first month of treatment for four antihistamines

Table 2 Incidence densities and number of reports of sedation with four antihistamines

		No of events			Incidence density			
Antihistamine	Cohort	N_1	N_2	N_A	ID_1	ID_2	ID_1–ID_2 (99% CI)	ID_A
Loratadine	9 308	15	2	19	2.6	0.4	2.23 (0.4 to 4.1)	1.2
Acrivastine	7 863	35	11	49	7.9	2.2	5.72 (1.8 to 9.6)	4.4
Fexofenadine	16 638	21	3	24	3.1	0.3	2.8 (0.9 to 4.6)	1.5
Cetirizine	9 554	53	9	68	8.5	1.2	7.30 (4.1 to 10.5)	3.7

N_1, ID_1 = number of events, incidence density during the first month of treatment.
N_2, ID_2 = number of events, incidence density during treatment months 2-6.
N_A, ID_A = total number of events, incidence density.

Table 3 Odds ratios for the risk of drowsiness and sedation associated with antihistamines

	Unadjusted		Adjusted for age and sex	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Loratadine	1 (baseline)		1 (baseline)	
Cetirizine	3.52 (2.17 to 5.71)	<0.0001	3.53 (2.07 to 5.42)	<0.0001
Fexofenadine	0.68 (0.38 to 1.22)	0.2	0.63 (0.36 to 1.11)	0.1
Acrivastine	3.27 (2.0 to 5.39)	<0.0001	2.79 (1.69 to 4.58)	<0.0001

What is already known on this topic

Second generation "non-sedating" antihistamines are usually considered to be equivalent in efficacy but their sedating properties are less clear

Prescription-event monitoring is a well established method of recording events experienced after routine prescription of drugs

What this study adds

Loratadine and fexofenadine resulted in a significantly lower incidence of sedation than cetirizine and acrivastine

No cardiotoxic events of relevance were noted for any of the four antihistamines studied

Prescription-event monitoring has various strengths and weaknesses.[5] The method is non-interventional and does not interfere with general practitioners' decisions about the most suitable treatment for a patient. It therefore avoids the selection bias inherent in clinical trials. It is carried out on a national scale and is representative of the whole population using the drug. As all events are monitored, the technique can pick up trends in events that might not be considered to be related to the drug by doctors seeing individual patients. Additional information, such as use during pregnancy, can be monitored, and data on the use of certain drugs during the first trimester of pregnancy have been published.[7] A disadvantage of the method is that it relies on general practitioners returning completed green forms. Thus there may be a bias caused by the lack of data from non-responders. However, there is no reason to suppose that any such bias would be different for the drugs compared in this study. Even though the data collection period for fexofenadine was later than for the other drugs, we are not aware of any publicity that might have affected the reporting of sedation. Also, there is unlikely to be any hidden confounding of these results, since all the drugs are prescribed for well defined, similar, indications. Adjustment for age and sex did not greatly alter the odds ratios.

Sedative effects of antihistamines

The number of reports of sedation with all four antihistamines was low. However, the adjusted odds ratios suggest that cetirizine was 3.5 times more likely and acrivastine 2.8 times more likely to result in reports of sedation than loratadine; there was no significant difference between loratadine and fexofenadine. Sedation might result in an increased risk of accident and injury, but we found no such difference between the antihistamines.

The second generation antihistamines are difficult to separate in terms of efficacy. Previous investigations have shown the potential cardiotoxic effects of astemizole, ebastine, and terfenadine which can, in serious cases, result in torsade de pointes.[3 4] Fexofenadine, a metabolite of terfenadine, has also been connected with cardiotoxicity,[8] although other reports suggest that this is not the case.[9] However, no cardiotoxic events of relevance were noted for any of the antihistamines in this study.

Our findings suggest that in situations in which even very infrequent reports of sedation are undesirable (for example, when prescribing for flight crew) loratadine or fexofenadine are preferable to acrivastine or cetirizine.

We thank all the general practitioners who completed and returned their green forms. Without their cooperation this investigation would not have been possible.

Contributors: RDM first noticed the relevant differences in reporting rates, did the initial analyses, wrote the first draft of the paper, and is the guarantor. GP was responsible for the data processing assisted by Gillian Pearce. ND undertook the final and independent statistical analysis. SS was responsible for the discussions balancing the statistical and clinical perspectives of the study

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Competing interests: The unit has received funds from Hoechst Marion Roussel and Schering Plough but there has been no external funding of the comparison reported in this paper.

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Commentary: Reporting of adverse events is worth the effort

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The paper by Mann et al relies on adverse event monitoring. Adverse events are undesirable things that happen to patients and include adverse reactions caused by drugs. Some schemes are limited to adverse drug reactions. The United Kingdom Committee on Safety of Medicines, for example, collects and analyses about 20 000 yellow cards each year. They have proved valuable in detecting adverse reactions,[1] and the system covers all drugs throughout their use and in all patients. It depends, however, on a reporter suspecting a reaction and having the confidence and time to commit the suspicion to paper.

Schemes that monitor events rather than reactions remove the need for individual practitioners to assess whether a relation might be causal. The Southampton "green form" scheme is a method of post-marketing surveillance in general practice.[2] It aims to discover adverse events occurring in patients prescribed a

selected new drug during a particular period of observation. The scheme is notified by the Prescription Pricing Authority of every prescription of the drug, and after a time sends a form to the prescriber, asking for notification of any adverse events reported by the patient to them. About half the cards sent out are returned. The collected data for a specific drug and event are used to calculate incidence density (the ratio of the number of reports of the event during treatment to the number of patient-months of exposure to the drug).[2] The relative risk of a given event across a group of drugs is estimated by comparing incidence densities.

The observational studies are, of course, not randomised and so may be biased.[3] For example, one preparation may be particularly used for a specific condition or age group, or there may be differential failure to detect, record, or report an adverse event. Estimates should be viewed with circumspection even if bias seems unlikely—several incidence ratios for many different events can be examined, and some will inevitably differ from others because of random variation. The associated significance will be misleading unless correction has been made for multiple comparisons. Results also have to be set in clinical context. We should certainly be reassured by the low overall incidence of sedation with selective histamine H_1 antagonists shown by Mann et al: fewer than one patient in 140 complained of drowsiness with any of these drugs. There are some differences between them, which may be relevant to people in safety critical jobs.

As the authors point out, the investigation would not have been possible without the cooperation of the reporters, who should be encouraged by seeing that their efforts are worth while. In due course, computerised systems such as the general practice research database may allow post-marketing surveillance without tears.[4,5] Until then, we will all benefit from the information that diligent reporters send on yellow cards and green forms.

Competing interests: The West Midlands Centre for Adverse Drug Reaction Reporting receives financial support from the Medicines Control Agency.

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A memorable patient

Keep looking for a reason

Sarah was 22 when she presented with the dreadful signs of a large space-occupying lesion deep in the dominant parietal lobe. She was drowsy with a severe headache, had severe dysphasia, and there was a significant rightsided weakness. The computed tomography said it all; a malignant intrinsic tumour at the trigone of the lateral ventricle, probably a glioblastoma.

She rallied a little on steroids overnight and so I performed a craniotomy, having suitably warned her worried family of the likely outcome and prognosis. I found a very bloody tumour that had some definition from the surrounding brain. The pathologist told me that the frozen section showed a highly malignant brain tumour, consistent with the radiologist's diagnosis.

The survival from this type of tumour in this position is measured in months, and there is no evidence that surgery does much more than relieve the pressure symptoms. Consequently, I completed a cautious internal decompression, stopped the bleeding, and closed up. She was unchanged, but bled into the tumour remnant the following day and I had to reopen the craniotomy. That night I was relieved that she was no worse.

Sarah's tumour was a gliosarcoma. This is a rare and even more malignant variant of a glioblastoma, in which it is thought that the new vessel forming factors released by the primary brain tumour induce sarcomatous change in the blood vessels. The news was not good.

Surprisingly, Sarah started to get better. Her speech improved and her hemiparesis almost disappeared. She was referred for radiotherapy and underwent the full six weeks' course. The follow up scan also looked good. She lost her job in insurance, but became a police receptionist.

Two years went by, but there was no sign of the tumour on further scans. By then, Sarah had become a good friend of the hospital, active in collecting money for the development fund, and talking to the press about her treatment.

After three years, when the vast majority of patients with a glioblastoma are dead, I asked the pathologists to review the case, but despite the tumour's unusual behaviour, they could not come up with any other diagnosis.

Meanwhile, Sarah had married and was thinking of starting a family. By this time, much more sensitive magnetic resonance imaging had become more freely available, and the scan showed no recurrence. At six years, I asked the pathologist to rereview the case. By now, immunocytochemistry was much more sophisticated, and despite the mitoses and other seemingly malignant features, he was able to reclassify the lesion as a much more benign pleomorphic xanthoastrocytoma.

When I told Sarah this exciting news, I was most surprised that it seemed unimportant to her, almost to the point of disinterestedness.

She remains well almost 10 years from diagnosis. Her scan is clear, but she still worries about recurrence. I worry about the possibility of radionecrosis which sometimes afflicts long term survivors of brain irradiation.

I have learnt three things from Sarah's case. Firstly, that having lived with the diagnosis of having had cancer but being free from recurrence, being an unusual statistic with a semibenign condition of unknown behaviour lacks meaning. Secondly, when tumours behave in highly unusual ways, keep looking for a reason. Thirdly, do not expect other patients' tumours to behave in a similarly unusual fashion—a temptation that I fell into at least once.

Michael Powell *consultant neurosurgeon, London*

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.