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ORIGINAL REPORT

Drug-Attributed Anaphylaxis

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SUMMARY

Allergic type I reactions to medicines range in their clinical presentation from rhinitis and urticaria to severe bronchoconstriction and anaphylactic shock. We examined all cases of suspected drug induced reactions classified as anaphylactic reactions or shock reported in Sweden between 1972 and 1995 with regard to patient characteristics and drug(s) suspected. Some comparisons with drug sales and prescription data were also made. During the study period of a total of 1338 reports concerned anaphylactic/oid shock or reactions with at least a possible causal relation to medicine giving an overall reporting rate of seven cases per million inhabitants per year of drug-induced anaphylaxis. Of these 1338 patients 51 (3.8%) died from their reactions. Among the non-fatal cases, 460 (34.4%) were diagnosed as shock and 827 (61.8%) as anaphylactic reactions. In total 46.3% of all reports concerned men but men were over-represented among the older patients and among the fatal cases (65%). There were 201 different drugs reported as 'suspected' them most common of which were dextrans (418 reports), X-ray contrast media (161 reports) and antibiotics (153 reports).

For dextrans the rate of anaphylactic reactions, shock and fatal cases reported were 128,101 and 21 per million bottles respectively. This decreased to 10.3, 9.8, and 0.4 per million bottles after the introduction of preventive treatment with dextran 1 in 1983.

The reporting rate for ionic contrast media were 0.14, 0.13 and 0.02 per 1000 l for reactions, shock and fatal cases respectively whilst for non-ionic contrast media they were 0.7/1000 l for reactions, 0.02/1000 l for shock, but there was no report of a fatal case. For phenoxymethylpenicillin the reported rate of anaphylaxis was 0.14 cases per million defined daily doses and for benzylpenicillin it was 3.7 cases per million defined daily doses. During the study period several drugs have been identified as important causes of anaphylaxis and measures have been taken to decrease the risk of anaphylaxis e.g. the introduction of preventive treatment with dextran 1, the shift from ionic to non-ionic contrast media and the abolition of polyethoxylated castor oil as a solvent. Spontaneous reporting of drug-induced anaphylaxis remains an important surveillance model but needs to be complemented by better quantitative methods. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — adverse effects; anaphylaxis

INTRODUCTION

Anaphylaxis is the most dramatic and potentially catastrophic manifestation of immediate (type I) hypersensitivity. This syndrome can affect virtually any organ in the body, although reactions involving the skin, the airways, the circulatory system and the gastrointestinal tract are the most common. Hypersensitivity to insect stings, certain food products and drugs are the most common causes of anaphylaxis. In a study from the United States[1] comprising a series of 32,812 consecutively monitored hospitalized medical patients, the frequency of drug-attributed anaphylaxis was 0.4/1000, and resulted in death in two of the 12 cases (16.6%). Epidemiological data on drug-attributed anaphylaxis however, is still sparse. Because of its rare occurrence it is difficult to obtain enough cases for a thorough evaluation of incidence and characteristics of this disease in cohort studies. Case–control studies are here more cost effective but even with

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this method it is hard to obtain enough cases and relevant controls since some of the offending drugs are rarely used. Moreover, some of the drug classes often involved in anaphylaxis like X-ray contrast media and dextrans are almost exclusively used in hospital. Disease and patient characteristics and some indication of frequency can be obtained through analysis of spontaneously reported cases compared to drug usage data. Such calculations are however rough and can easily be distorted by bias.

Previously, one series of dextran attributed cases of anaphylaxis reported in Sweden indicated that the risk of such reactions decreased after introducing preventive treatment with low-molecular dextrans (dextran 1).[2] A series of spontaneously reported cases of fatal anaphylaxis has recently been published from Denmark[3] describing the drugs most commonly suspected for such reactions. In the present investigation, characteristics of 1338 spontaneous reports of drug-attributed anaphylaxis submitted to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) 1972–1995 are analysed in relation to sales and prescription data.

METHODS AND SUBJECTS

The Swedish drug monitoring system

Reporting of suspected adverse drug reactions to SADRAC started in 1965 and has been mandatory since 1975 for fatal, other serious, new, unexpected or remarkable reactions. The reporting forms contain patient characteristics including age, sex, diagnosis, a medical history, routine laboratory data, and drug information including drug names, dates started, dosage and route of administration, frequency of administration, date drug use was discontinued, and detailed description of drug attributed adverse events. All reports are scrutinized for completeness by a pharmacist or a nurse who also carry out the primary evaluation. The reports are then discussed by a working party containing physicians, and the final evaluation is made by the full Swedish Adverse Drug Reactions Advisory Committee which comprises clinical specialists in relevant areas and clinical pharmacologists. For all fatal cases and most of the other serious cases complete medical records are requested. The following classification was used in this study: 'P' implies a possible, probable or certain causal relationship whereas 'N' denotes reactions judged as unlikely or unclassifiable. The WHO criteria were used for causality classification.[4]

Computerized total sales of drugs in Sweden started in 1972 and the data are available as so-called defined daily doses (DDD) or number of dosage units.

Terms investigated

The Swedish ADR terminology contains the following terms which can be expressions of immediate hypersensitivity: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction and anaphylactoid shock, bronchospasm, asthma, asthma aggravated, urticaria 'Quincke's oedema', angioneurotic oedema, and acute hypotension. Here we only included cases classified as anaphylactic and anaphylactoid reactions and shock. The terms anaphylactic/oid are used when symptoms from more than one organ system occur e.g. urticaria and bronchoconstriction. In general 'anaphylactic' is used for situations were IgE antibodies to the drug class have been demonstrated and anaphylactoid for situations where it is thought that the reaction is elicited directly by cascade phenomena. Shock is used where there has been a marked hypotension and impaired consciousness. The occurrence of antibodies are however seldom reported for the single case and therefore this distinction is imprecise and for the purpose of this investigation unnecessary.

RESULTS

General review

During the period of 1972 through 1995, SADRAC received, scrutinized and computerized a total of 6005 reports of any of the terms that could be elicited by type I hypersensitivity reactions and of these, 1338 reports concerned anaphylactic/oid shock or reactions. Of these 1338 patients, 51 (3.8%) died. Among the non-fatal cases, 460 (34.4%) cases were diagnosed as anaphylactic shock and 827 (61.8%) as anaphylactic reactions. Fig. 1 shows the number of reports per year. A total of 619 reports (46.3%) concerned males and 713 females. In six cases the gender was not reported. The age distribution is shown in Fig. 2. There were 201 different drugs reported as 'suspected'.

The top-ten drug groups were:

1. Plasma volume expanders
2. Contrast media

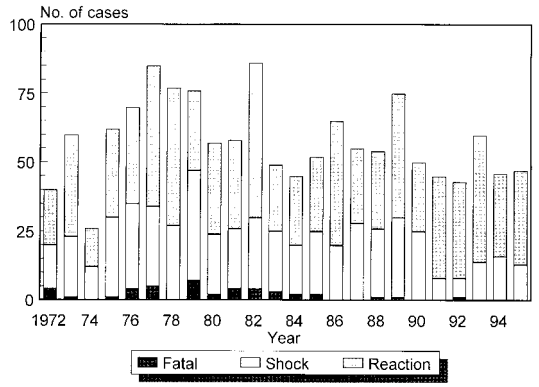

Fig. 1 — Number of cases of 'anaphylaxis' reported in Sweden 1972–1995

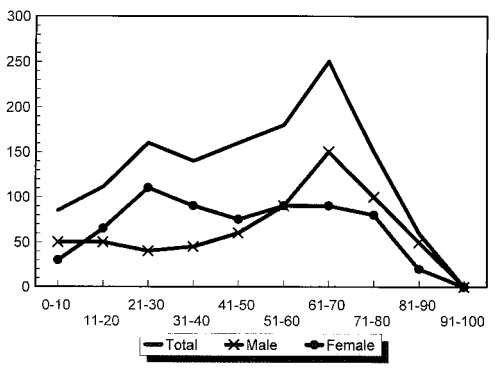

Fig. 2 — Age and sex distribution for cases of anaphylaxis reported in Sweden 1972–1995

3. Beta-lactam antibacterials
4. Anaesthetics, general
5. Allergens
6. Cytostatics
7. Anti-inflammatory/antirheumatic products, non-steroid
8. Anaesthetics, local
9. Antithrombotic agents
10. i.v solutions

Fatal cases

Of the fatal cases, 33 (65%) were male and 47 (92%) patients were more than 50 years old (Fig. 3). These proportions were higher than in the general population (49.4 and 33% respectively). The cases fatality rate was significantly higher in men than in women (5.3% (33/619) versus 2.5% (18/713), $p < 0.05$) and it increased with age from 1.5% in those under 49 years of age to 17.5% in

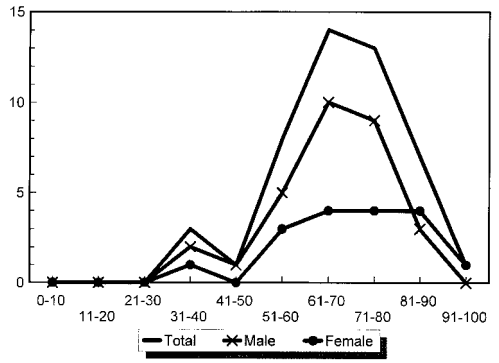

Fig. 3 — Age and sex distribution for 51 cases of fatal anaphylaxis reported in Sweden 1972–1995

those aged 80 years or more. Fifteen drugs were reported as 'suspected' in the 51 fatal cases. In 49 of these patients only one drug was suspected, one patient had taken two suspected drugs and another had taken three. Dextrans were the most common offending drugs (32 cases, 59%) and radiographic ionic contrast media were the second most common (11 cases, 20%), (Table 1).

Anaphylactic shock cases

Of 460 anaphylactic shock cases, 225 (49%) were male and 235 (51%) were female. Two hundred and eighty-four (62%) patients were over 50 years of age. There were more males than females (162 versus 122) in the older age group, whereas more females than males (114 versus 62) were in the age groups below 50 years.

One hundred and one different drugs were reported as 'suspected'. The most common offending drug were dextrans (175 cases, 34.5%), radiographic ionic contrast media (58 cases, 11.4%, and penicillins (44 cases, 8.7%). The reporting frequency of the main drugs and drug groups are shown in Table 1.

Anaphylactic reaction cases

Of 821 anaphylactic reaction cases, 361 (43.6%) patients were male. There were 347 (42%) cases in the age group over 50 years. This proportion was still higher than that in the Swedish population (33%). In the age groups over 50 years, 175 (48.5%) patients were male, whilst 40% were males in the below 50 years groups.

The pattern of drugs reported was similar to the shock cases with dextrans (213 cases, 24.3%), contrast media and penicillins (63 cases, 7.1% and 77 cases, 8.8%). In total, 174 different 'suspected' drugs were reported (Table 1).

Reports in relation to drug sales

During the period 1972 to 1982, dextrans sales were 1,461,015 bottles (500ml/bottle) and the reported frequency of anaphylactic reactions, shock and fatal cases were 128,101 and 21.2 per million bottles respectively. In the period 1983 through 1992 the dextrans (excluding dextran 1) sales increased to 2,338,000 bottles, however, the reported frequency decreased to 10.3, 9.8 and 0.4 per million bottles, respectively.

For contrast media, the total sales of ionic agents were 439,477 l and the reported frequencies were 0.14, 0.13 and 0.025 per 1000 l of anaphylactic reaction, shock and fatal cases, respectively. Whereas, the total non-ionic agents sales reached 343,7334 l and the ratios were 0.07 and 0.02 reports per 1000 l on anaphylactic reaction and shock reports, respectively. No fatal case was reported for non-ionic agents.

Among the antibiotics, sales of benzylpenicillin and phenoxymethylpenicillin was 6.8 and 390 million DDDs respectively giving a reported incidence of anaphylaxis of 3.7 and 0.14 per million DDDs, or 192.3 and 7.3 per million treatment weeks.

DISCUSSION

The 1338 cases of anaphylaxis reported during this 24-year period constitutes a reported rate of seven cases per million person years which is about as rare as the incidence of agranulocytosis found in an epidemiological study.[5] The case fatality rate in anaphylaxis (3.8%) is however lower than for agranulocytosis (9%).[5] In Sweden, the proportion of all incident cases of agranulocytosis that are actually reported is high, 30–80%.[6,7] For anaphylaxis there are no investigations into what proportion of all cases that are reported they comprise but we assume it to be lower than for agranulocytosis since many mild cases are treated outside hospital. Thus, the present estimate most probably is too low.

In the present study slightly more females than males were reported to suffer anaphylaxis in general. In contrast, more males were reported to develop fatal anaphylaxis (1.8/1). This may be due to the fact that women in general consume more medicines than men but that in the higher age groups, where the case fatality is higher, exposure to high risk drugs may be different especially exposure to dextrans and radio-contrast media. The higher fatality rate in the older patients is logical considering the increased co-morbidity and increased sensitivity to hypotension.

In the present investigation the most commonly implicated drug group in the development of anaphylaxis were dextrans, which as 'suspected' offending drugs constituted 24%, 34% and 59% in reaction, shock and fatal case categories, respectively.

However, since the introduction of low molecular dextran 1 (which occupy the binding sites of dextran reactive antibodies) in 1983, the reported incidence of severe anaphylactic reactions has decreased markedly.[2] Dextrans have been used for volume replacement, prophylaxis against thrombosis and improvement of the micro circulation for nearly 40 years in Sweden. The present data have further confirmed[2] that by application of dextran 1, dextrans can be safely used.

The most common agents causing anaphylaxis were radiographic contrast media. Of these, 63 anaphylactic reactions (73.3% of all contrast media), 58 cases of shock (90.6%), and 11 fatal cases (100%) concerned ionic agents.

The true incidence of anaphylaxis cannot be calculated from the present data. It is especially complicated to evaluate a comparison of the reported rates of ADRs for different drugs because of time trends in reporting and the possibility of selective reporting. In the case of ionic and non-ionic contrast media no DDDs exist and therefore we are limited to the number of litres sold. The reporting rate over time could be influenced by changing dosage routines. The comparison between ionic and non-ionic contrast media can also be influenced by the average amount used of the respective group of contrast media. However, we have never seen a situation of 'biased reporting' in which 'fatal cases' have disappeared after a change in the drug use pattern or reports in the literature. Since the non-ionic contrast media are newer a higher reporting rate for this group would be expected. Some previous studies held the view that low-osmolar non-ionic agents reduced only minor to moderate ADRs, but were unable to demonstrate a decrease in severe ADRs[8] and there was little

evidence of saving lives.[9] However, in a large-scale (337,647 patient), nationwide cohort study on adverse drug reactions (ADRs) to high-osmolar ionic contrast media and low-osmolar non-ionic contrast media performed in Japan,[10] the overall incidence of ADRs was 12.7% in the ionic contrast media group and 3.1% in the non-ionic contrast media group and severe ADRs occurred in 0.22% of the ionic and 0.04% of the non-ionic contrast media, a five-fold difference. In our studies, the ratio was also about five-fold and the difference 1.6 cases per 10,000 l.

Antibacterials were the third most common agents reported in the present study. Among the 163 reported cases only two patients died, one after an injection of benzylpenicillin and one following co-trimoxazole. In relation to sales the 'incidence' of reported anaphylaxis to phenoxymethylpenicillin was seven cases per million treatment weeks with an equal distribution between shock and reactions. For benzylpenicillin the same estimate was 26 times higher and the only fatal case occurred after an injection. The general view that most penicillin-attributed cases of anaphylaxis occur when the drug is given parenterally [11–13] is supported in this study.

The relatively new fluoroquinolone antibiotics do also appear in this material and of the 10 cases five were attributed to norfloxacin which is the most widely used fluoroquinolone in Sweden, three cases were reported involving ciprofloxacin which is also widely used but two cases were reported to involve temafloxacin during a period when only about 30,000 prescriptions had been filled.

Some other drugs seem worthy of comment: asparaginase, streptokinase, diazepam, propanidid, and chlorhexidine. Asparaginase is an enzyme which catalyses the breakdown of asparagine and which can inhibit the growth of malignant cells unable to synthesize asparagine. Because of its protein nature, it is not surprising that anaphylaxis and other hypersensitivity reactions can be induced. Streptokinase os a non-enzymatic protein that is used widely as a thrombolytic agent. The frequency of allergic reactions to streptokinase has previously been reported from large postmarketing studies.[14,15] In these studies the focus was on serious reactions which are rare. Recently it was recognized that hypersensitivity reactions to streptokinase were fairly common and usually mild.[16] In that review, however, no clear separation of different types of hypersensitivity reactions was made.

Thirteen of a total of 15 cases of anaphylaxis to diazepam were reported for parenteral use of a preparation that contained polyethoxylated castor oil.[17] The propanidid products implied in the reports were also provided as a liquid dissolved in polyethoxylated castor oil. Anaphylactoid reactions associated with this vehicle led to its general withdrawal from use in February 1984.

Anaphylaxis associated with chlorhexidine has previously been reported in the literature.[18] The nine cases described in this report occurred both in connection with use on the oral mucosa as well as when used as a skin disinfectant. Although this seems to be a rare reaction it is of value to know that this type of reaction can occur with topical application of chlorhexidine.

During this study period several drugs have been identified as causes of anaphylaxis and in most instances through spontaneous reports. Several measures have been taken to decrease the risk of anaphylaxis e.g. the development of dextran 1 which by binding the antibodies clearly decreases the risk[2] development of non-ionic X-ray contrast media, and the elimination of polyethoxylated castor oil as a solvent. It is important to continue to monitor new chemical entities and new products through spontaneous reporting. It is however mandatory to complement this system with better methods of estimating the size of the risk by more rigorous analysis. Examples are *ad hoc* case–control studies or maybe ongoing case–control surveillance. In some instances a case–population approach may suffice but this method has to be better validated before it can be generally recommended.

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