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BACKGROUND NOISE IN HEALTHY VOLUNTEERS – A CONSIDERATION IN ADVERSE DRUG REACTION STUDIES

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Abstract: In adverse drug reaction studies proper control over 'Back ground noise' is to be maintained to avoid erroneous conclusions to be drawn for adverse drug effects. Healthy volunteers, not taking any medication, were surveyed by a questionnaire to obtain data on the occurrence of any symptoms, often ascribed to side effects of drugs. Only 62 subjects out of a total of 236 (26.27%) stated experiencing none of these symptoms during the previous 3 days. The remaining subjects reported some symptoms, with an median number of symptoms experienced per person being 2; the most common being fatigue; headache, inability to concentrate and excessive sleepiness.

Key words: background noise healthy volunteers non-drug adverse effects

INTRODUCTION

Adverse Drug Reaction (ADR) detection studies reported by Boston Collaborative Drug Surveillance Program, and Adverse Drug Reactions Advisory Committee, Aberden Dundee (1–3) were carried out on a large scale. Many adverse effects have been identified like agranulocytosis with chloramphenicol, thromboembolic events with oral contraceptives, oculomucocutaneous syndrome with practolol, Guillain Barre' Syndrome with zimeldine, hepatic disorders with benoxaprofen, anaphylactoid reaction with zomepirac etc (4-9). In our country, the subject of Adverse Drug Reaction monitoring is yet in its infancy; and centres in Chandigarh, Bombay, Manipal, Srinagar and Aligarh have undertaken initial steps in this direction.

In the studies of ADRs, several factors including temporal relation, dechallenge, rechallenge etc. are to be taken care of (10). Pogge et al (11) reported ADRs to the act of medication itself used as a placebo. Moreover adverse symptoms have also been reported in healthy volunteers (12) who were neither suffering from any disease nor taking any medication. Therefore, proper controls, like avoiding the effects of background noise, are to be maintained. Otherwise there may be the risk of wrongly ascribing certain symptoms as adverse reactions to a drug.

Recently a few ADR detection studies have been reported in India (13-16). None of these compared the incidence of increase in symptoms following treatment as compared with those which were present before starting the treatment.

The present study was undertaken to record the background noise, without the use of any drug.

METHODS

Medical students of 1st and 2nd year at the Govt. Medical College, Patiala, were surveyed by a questionnaire, to obtain data on frequency of some symptoms, often listed as side effects of drugs as described by Reidenberg et al (12), without giving them any medication. The student volunteers were asked to check on a questionnaire form any of the listed symptoms that they had experienced during the previous 72 hrs. In addition each one was asked to list any disease he/she had and any drugs taken during that period. Data from each questionnaire was transferred to a Masterchart and counted for tabulation of each item.

RESULTS

Of the 296 volunteers, 60 (20.3%) either had an illness or had taken medications, so they were excluded from the study. Of the remaining 236, 35% were males

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and 65% females, belonging to the age group of 18-23 years. The percentage of volunteers reporting any of the symptoms are listed in Table I. Only 62 out of 236 subjects (26.27%) stated that they had experienced none of the 25 symptoms listed, or any other symptom during previous 72 hours. Of the remaining 174 volunteers, one symptom was experienced by 41 (17.37%), two by 51 (21.61%), thereby 33 (13.98%), and more than three by 49 (20.76%). Four most common symptoms occuring were fatigue (in 25.84%), Headache, inability to concentrate (each in 25%) and excessive sleepiness (in 23.3%). The median number of symptoms experienced per person comes to 2.

In addition to the list of 25 symptoms included in the questionnaire, students were asked to report any other symptom experienced by them. Table II shows the incidence of such symptoms.

Data of the volunteers who were either suffering from a disease or taking any medication which were excluded from healthy volunteers analysis, was also analysed separately. The median number of adverse symptoms per person in this group was 4.

TABLE I: Percentage of volunteers reporting each symptom.

Symptom	*Incidence*	*Symptom*	*Incidence*
Fatigue	25.84%	Insomnia	5.5%
Headache	25%	Nausea	5.08%
Inability to concentrate	25%	Bleeding gums after brushing	5.08%
Excessive	23.30%	Nasal congestion	4.23%
Sleepiness		Skin rash	4.23%
Irriability	11.01%	Pain in joints	2.96%
Giddiness	9.32%	Diarrohoea	1.69%
Urticaria	8.89%	Vomiting	1.27%
Bad Dreams	8.47%	Bleeding/Bruising	1.27%
Pain in Muscles	8.47%	Palpitation	0.84%
Loss of appetite	8.05%	Fever	0.42%
Constipation	6.35%	Excessive bleeding	
Fainting/dizziness	6.35%	from gums after brushing teeth	0.42%
On 1st standing up			
Dry mouth	5.93%		

Note: Symptoms with an incidence of more than 10% are underlined.

TABLE II: Other symptoms experienced.

Symptom	*Number of volunteers*	*Symptom*	*Number of volunteers*
Ulcers in Mouth	1	Excessive sweating	1
Eyes:			
Tiredness	1	Occasional cough	1
Pain	1	Skin spots	1
Irritation	1	Burning sensation in epigastrium.	1
Strain	1	Pain on movements	1
Feeling of fainting on prolonged standing	2	Irritation in throat	1

DISCUSSION

In our country, the subject of monitoring is relatively lagging behind; possibly due to absence of central registration authority where records of all prescriptions are retained, lack of specific infrastructure, improper maintenance of records, simultaneous use of multiple therapies by the patients, lack of awareness, and lack of clinical pharmacologists.

A variety of symptoms can be caused by a disease or any of its treatments. Bulpitt et al (17) have shown common adverse symptoms in normal persons, untreated hypertensives, and treated hypertensives. Many of these were previously wrongly ascribed as side effects of anti-hypertensive therapy. Reidenberg et al (12) have reported adverse non-drug effects in healthy volunteers.

Although many studies on ADR detection have been conducted in our country, we have not come across any study on non-drug-adverse-effects in healthy volunteers.

The present study indicates that positive history of many symptoms, commonly considered as side effects of drugs, can be elicited even from healthy volunteers. The frequency of some of these symptoms depends on the environment, physical health and emotional state of the subject and on the intensity with which the examiner searches for the symptoms (11).

Stephen et al (18) have discussed advantages, disadvantages and differences due to diffeent methodology adopted i.e. patient's diary card questionnaire, checklist and standard questions. They have suggested that if the adverse symptoms before and after the treatment cannot be distinguished qualitatively, then the correct quantitative procedure is to compare them using non-parametric statistics giving the confidence limits for the incidence of ADRs.

Although the present study shows many common non-drug adverse effects, it cannot be used as objective standard for comparison with other studies due to following reasons :

1. The study population was selective and not generalised as seen in clinical practice.
2. It had more female participants than males.
3. In clinical set up disease process could itself modify the symptoms.
4. In retrospective recollection of symptoms, patients are likely to forget some of the self-experienced symptoms, whereas in a prospective study, they are less likely to do so.
5. Many biochemical abnormalities, signs and symptoms which could have been considered as ADR were not included in this study.
6. This study excluded students who had taken any drug. Many among these had taken self-medication as sympatomatic treatment. Their symptoms were excluded from tabulation suspecting these to be associated with disease or the drugs consumed. But it is possible that those symptoms for which they took the drugs could be present as such rather than being due to a disease or the drugs consumed, thus lowering the actual incidence of these symptoms in our study.

It is thus concluded that symptoms resembling ADRs, are present even in healthy volunteers as background noise. Thus in any ADR study, background noise should be recorded before starting treatment and compared with the incidence of these symptoms appearing after start of treatment.

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