

DRUG-INDUCED REACTIONS IN STOMATOLOGY

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ABSTRACT

The huge importance of adverse reactions to drugs for public health is well proven. Any drug can produce side effects, and any of these reactions can have an oral manifestation. We have organized a pharmacoepidemiologic study to describe the drug-induced reactions manifested in the oral cavity in hospitalized patients (admitted in the Vth Internal Medicine Clinic) and in outpatients (consulted and treated in dental offices). For assessing side effects, the Adverse Drug Reaction Probability Scale was applied. 67 drug-induced oral reactions were described in the studied patients. The frequency was higher in women, in the elderly and in case of polypragmasia. The drugs most frequent incriminated in oral adverse reactions have been NSAIDs, antihypertensives, statins, antibiotics, corticoids and antidepressants. The most frequent reactions have been oral allergic reactions, xerostomia, stomatitis and abnormalities of taste. The best way of preventing and detecting oral side-effects is a team made up by dentists and doctors of different specialties.

Keywords: side effects, oral reactions, pharmacoepidemiologic study

INTRODUCTION

Adverse reactions to drugs (ADR) are an assumed risk, since so many studies have proven their huge importance for public health. In USA for example, where FDA is very active in evaluating the amplitude of drug iatrogenesis, it is estimated that 700,000 emergency department visits and 120,000 hospitalizations are due to ADR annually, \$3.5 billion is spent on extra medical costs of ADR annually and at least 40% of costs of ambulatory ADR are estimated to be preventable [1,2,3]. It is presumed that the number of adverse drug events will increase in the next years because of the development

of new medication, the discovery of new uses for older medication, the aging process of the population and the increase in drugs for disease prevention.

ADR can involve any organ and system and has a very polymorphic way of expressing. Practically any medication can produce side effects, and any of these reactions can present with an oral manifestation.

The continuous collaboration between medical specialties and dental ones can help better estimation, prevention and treatment of drug-induced reactions in stomatology.

MATERIAL AND METHODS

Continuing a previous experience on this subject [4], we have organized a pharmacoepidemiologic study that aimed to find out and describe the drug-induced reactions manifested in the oral cavity in hospitalized patients and in outpatients. The hospitalized patients were admitted in the Vth Internal Medicine Clinic between 2011-2013; the outpatients were consulted and treated in dental offices.

The research team was made up by dentists and doctors of different specialties: internal medicine, geriatrics-gerontology, clinical pharmacology and by dental medicine students.

When an adverse reaction manifested in the oral cavity was suspected, the Adverse Drug Reaction (ADR) Probability Scale was applied. This scale was developed to help standardize assessment of causality for all adverse drug reactions, being simple to apply and widely used. It consists of 10 questions that are answered as either Yes, No, or "Do not know" and different values (-1, 0, +1 or +2) are assigned to each answer. We used the simplified version that uses the following 10 questions:

1. Are there previous reports of this reaction?
2. Did the adverse event appear in a reasonable time after the drug was given?
3. Did the adverse reaction improve after drug discontinuation?
4. Did the adverse reaction reappear when readministering the drug?
5. Were there other possible causes for the reaction?
6. Did the adverse reaction reappear upon administration of placebo?
7. Was the drug detected in the blood or other fluids in toxic concentrations?
8. Was the reaction worsened by increasing the dose? Or, was the reaction diminished by decreasing the dose?

9. Did the patient have a similar reaction to the drug in his personal history?

10. Was the adverse event confirmed by other objective evidence?

The reaction was considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less. [5].

RESULTS AND DISCUSSIONS

1330 patients were examined, with the following distribution of age and sex (fig. 1).

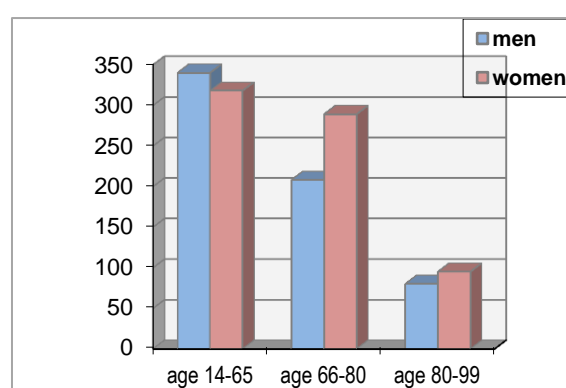


Figure 1. Distribution of patients according to age and sex

We have found 67 drug-induced oral reactions in the studied patients. We took into account reactions with the score of Adverse Drug Reaction (ADR) Probability Scale higher than 3, that is those that were possible, probable or very probable.

Out of these, 56% were taking a treatment for chronic diseases, and 34% were exposed to polypragmasia. We didn't voluntarily readminister the drug, except for the 12 cases in which the adverse reaction hasn't been recognized in the beginning.

The distribution of the side-effects in the studied patients showed a higher proportion of the side-effects in women and in the elderly (especially those with age > 80) (fig.2).

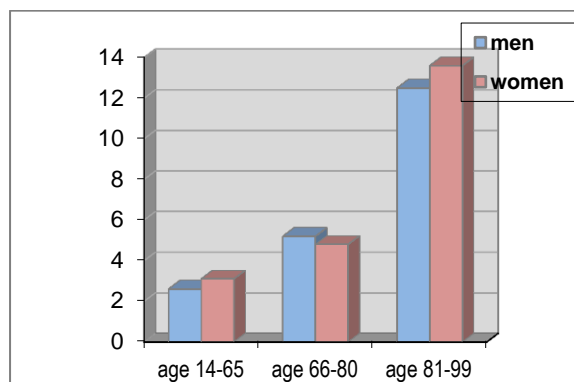


Figure 2. Proportion of side-effects in different categories of age and sex

These reactions had the following clinical expressions:

1. Oral allergic reactions:
 - a. Caused by systemic medication: 26 cases, proving an increase compared to the previous data (22 cases in the previous study) and confirming the general reported tendency [6]. We have noticed erythematous eruptions, more frequent occurring on the gingiva, buccal mucosa and lips. The lesions appeared in the first 24 hours of administration in 24 cases, and the incriminated drugs have been: barbiturates (6 cases), NSAIDs (9 cases), salicylates (5 cases), sulphonamide (4 cases). In 2 cases a delayed reaction was noticed, that appeared after 10 days of ampicillin administration. In all cases the withdrawal of the causative drug led to complete resolution of the lesions.
 - b. Oral contact allergic reactions:
 - 3 cases, manifested as inflammation of the buccal and labial mucosa, in asthmatic patients that used inhaled corticosteroids: budesonide, beclomethasone;
 - 3 cases of gingivo-stomatitis appearing in contact with alendronate (1 case), mouthwash (1 case), toothpaste (1 case).
2. Aphthous-like ulcers, resembling to recurrent aphthous stomatitis, were found in 6 cases, that were highly probable produced by alendronate (1 case), bisoprolol (1 case),

losartan (2 cases), olanzapine (1 case), sertraline (1 case). The ulcers healed simple discontinuation of the treatment.

3. Glosodinia appeared in 3 cases, incriminated drugs being captopril (1 case), enalapril (2 cases).

4. Glossitis was described in 5 cases, and the causative drugs have been atorvastatin (3 cases), venlafaxine (2 cases).

5. Erythema multiforme was rare, appearing in 2 cases, with ciprofloxacin and sertraline. One case had symmetrical erythematous edema on the oral mucosa, while the other associated bullous lesions. Both cases were accompanied by skin eruption. The evolution was mild, with decrease of oral and skin lesions in 10, respectively 12 days after withdrawal.

6. Oral ulcerations appeared in 2 cases because of oral irritation caused by aspirin and olanzapine.

7. Oral lichenoid reactions were described in 3 cases, after use of enalapril, metoprolol, naproxen.

8. Gingival hyperplasia was produced in one case of long use of nifedipine and in a chronic use of an oral contraceptive and completely disappeared after withdrawal.

9. The 6 cases of xerostomia were caused by use of atenolol (1 case), sotalol (1 case), benzodiazepine (1 case), pregabalin (1 case), olanzapine (1 case), venlafaxine (1 case). The patients had severe decrease of salivary flow rate, with destructive effect on dental health, which required replacement of causative drug and long term stomatologic treatment.

10. In 6 cases abnormalities of taste (hypogeusia and dysgeusia) were produced by atorvastatin, simvastatin, loratadine, metoprolol, riluzole.

The higher frequency of the side effects in women is in accordance with known data [7]. The adverse reactions were also higher in the elderly, their increased susceptibility to

iatrogenic disease being well known [8], and also their higher consume of drugs that lead to oral side-effects such as NSAIDs, antihypertensives [9, 10, 11].

In the elderly severe drug effects such as erythema multiforme, severe allergic reactions were also more frequently noticed.

The drugs most frequently incriminated in oral adverse reactions have been NSAIDs, antihypertensives, statins, antibiotics, corticoids and antidepressants. Although the severity of the reactions was generally mild, the patients had already withdrawn the suspected medication 2-3 days before they had been consulted, because of the discomfort which altered their quality of life. It is very important to detect the possible oral side effects as soon as possible and replace the incriminated medication, considering the risks of a sudden withdrawal in case of antihypertensive therapy for instance. We don't consider as recommended re-administration of a suspected drug, taking into account that a second reaction could be much more severe.

The drugs that we incriminated have already been known as potential offenders for oral cavity [12], yet the diagnostic of the side effects wasn't an easy task, because in many cases the clinic aspect is very likely to other common diseases. A careful history for every

patient is very important, and sometimes even his family history is needed (searching for other allergic reactions). Working in a complex team (doctors, dentists and clinical pharmacologists) is also important, as well as continuous information about the safety of new therapies. Patients unaware of their oral problems were the most difficult to evaluate, and so have been at a higher risk for preventable side effects.

CONCLUSIONS

1. Our study proves that oral drug-induced reactions are an important health problem, being frequently described in hospitalized patients and also in outpatients.

2. The frequency was higher in women, in the elderly and in case of polypragmasia.

3. The drugs most frequent incriminated in oral adverse reactions have been NSAIDs, antihypertensives, statins, antibiotics, corticoids and antidepressants.

4. The most frequent reactions have been oral allergic reactions, xerostomia, stomatitis and abnormalities of taste.

5. The best way of preventing and detecting oral side-effects is a team made up by dentists and doctors of different specialties: internal medicine, geriatrics-gerontology, clinical pharmacology.

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