THE SIDE EFFECTS OF DRUGS ON THE GASTRO-INTESTINAL TRACT AND THE LEVEL OF IMMUNOGLOBULINS IN CASES OF DYSPEPSIA FOLLOWING ANTIRHEUMATICS

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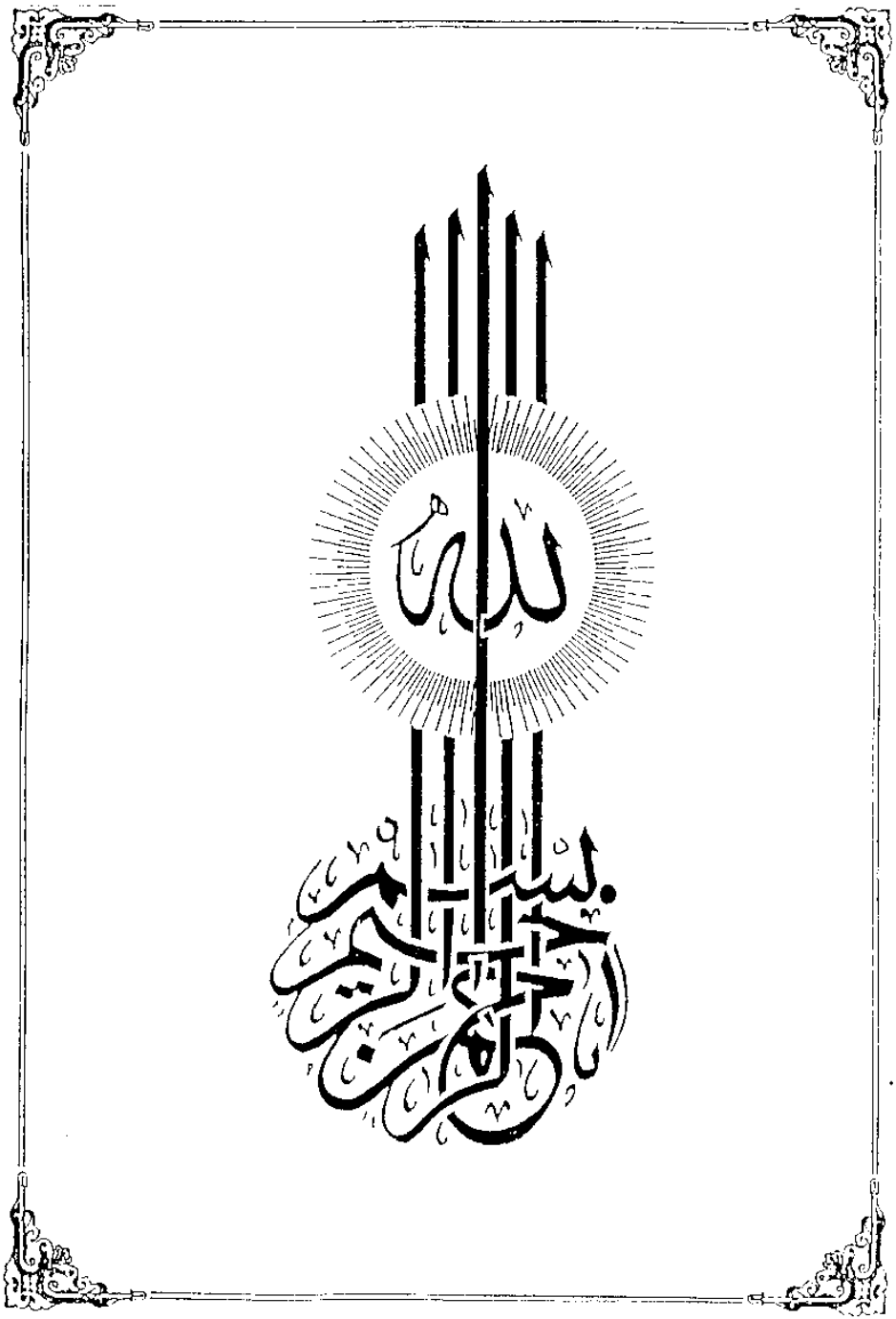

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INTRODUCTION

Nowadays much attention has been focused on the morbidity and mortality attributed to the use of prescription medications. It has been widely claimed that reactions to drugs have become a major cause of hospitalization, prolonged hospital stays and even death, with projections of up to 140,000 deaths annually in the United States from A.R_s to drugs. Clearly if these projections are valid, A.D.R_s constitute a major medical problem. (Fred E.Karch, and Louis Losagna, 1975).

What is an A.D.R_s ?

The world Health Organization has suggested that an A.D.R_s is any response to a drug which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis or therapy. Although these criteria for evoluating A.D.R_s seem clear, there are major difficulties in discerning whether a particular event in a given patient is the result of a specific medication or part of the patient's under lying illnesses. The problem is further complicated by the fact that most patients who experience drug reactions often have been receiving many medications and frequantly have several under lying illness that might account for the particular symptoms attributed to the drug. Also many of the symptomatic complaints often attributed to drugs as nausea for example

is totally subjective.

(Fred E. Karch, and Louis Losagna, 1975).

The body systems most frequently affected by adverse drug reactions according to cluff's study (1964) of 714 hospitalized patients over a 3 months period at John Hopkins Hospital, was the gastrointestinal tract 35.6%. Stewort F. Alexander (1971) said that gastrointestinal reactions to medications are the ones most frequently observed and fortunately they are usually the least hazardous. Many of them diarrhea, nousea, vomiting were minor drug reactions. Nevertheless if these minor reactions are sufficiently exacerbated, they can readily incapacitate and sometimes seriously harm a patient. Such minor reactions may also be indicators of more serious reactions that are developing or have developed.

Mechanisms of the drug reactions :

George J. Caranasas (1974) mentioned that adverse reactions were divided into those resulting from the pharmacological effects of drugs and those probably due to drug allergy 17.6% of the patients reactions on admission were due to probable or possible allergic mechanisms.

The adverse effects can be divided into 2 kinds:

(1) One type is due to an exaggeration of the desired pharmacological action (too much drug fixed to

primary sites of action) or to an unwanted pharmacological action (too much drug at other than primary sites of action).

(2) The second type involves structural or biochemical damage of the cell.

Incidence :

(1) Age :

During 3 year period of study (Aug. 1969 : July 1972) in the University of Florida Teaching Hospital George. J. Caranosas found that propartionately fewer admission for drug induced illness were observed in patients under 61 years of age, but between 61 and 80 years of age proportionately more patients were admitted because of drug reactions. The higher incidence of drug reactions in older individuals may be due to the use of a greater number of drugs that increase the likelihood adverse reactions in the elderly. In the 1st few weeks of life the renal clearance of drug is relatively lower than in adults, the liver is deficient in drug metabolising enzymes and the elimination of several drugs is impaired. The protein binding capacity for drugs is lower than in adults and there is an increase sensitivity of immature tissues to some drug effects. The newborn child particularly if premature is therefore more susceptible to certain adverse drug effects.

Age Range Year	Adverse drug reaction admissions
11 - 20	6.2 %
21 - 30	10.7 %
31 - 40	11.3 %
41 - 50	11.9 %
51 - 60	18.6 %
61 - 70	24.9 %
71 - 80	14.7 %
81 - 90	1.7 %

(2) Race, Sex :

Adverse reactions occur more frequently in whites than in blacks and in women than in men. This is may be because women tend to take more drugs, but these studies not demonstrate other factors possibly responsible for the sex differences noted. (George J. Caranasas, 1974).

	Male	Female	Total
White	30.5 %	50.3 %	80.8 %
Black	6.2 %	13.0 %	19.2 %
	36.7 %	63.3 %	100 %

(3) Route of Drug Adminstration :

Adverse reactions to drugs occur more often in patients are given the drugs orally.

(4) The incidence increases with an increase in the number of medication administered, and in the length of time they are administered. (Smith, 1966).

(5) Three quarters of the patients with allergic reactions to drugs has ulcer, ulcerative colitis or gastrointestinal neoplasms.

Avoiding Adverse effects :

(1) Decreasing the rate of

(2) Decreasing the frequency of administration by the use of prolonged action.

(3) Buffering to the optimum PH before ingesting, injecting or applying topically to sensitive surfaces.

(4) Adjusting the tonicity to that of the appropriate body fluid.

(5) A chieving appropriate rates of dissolution and absorption of drug administered orally in solid dosage forms.

(6) Administering the minimum effective dose for the shortest possible period of time.

(7) Monitoring closely the blood levels of toxic durgs, particularly those that are hepatotoxic.
(Stewort F. Alexander, 1971).

- In a regional approach to gastrointestinal reactions to drugs one turns to :

- Oral cavity
- Pharynx
- Stomach
- Large intestine
- Liver, Biliary system
- Peritoneum.
- salivary glands.
- oesophagus.
- small intestine.
- Pancreas.
- Spleen.

CHAPTER I

ORAL CAVITY AND SALIVARY GLANDS

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1. Dry Mouth :

- Lourence (1973) said that atropin and other anticholinergic drugs are capable of reducing all secretions of Exocrine glands including salivary glands leading to dry mouth. Atropine acts by competing for the same drug receptors as acetyl choline, occupying them and thus rendering the acetyl choline ineffectual.

- Meyler (1972-1975) found that antihistamines lead to dryness of the mouth, and this is attributed to an atropine like action possessed by many antihistamines, it is prominent with deptropine and diphenyhydramine.

- Also Mizgala, H.F. (1976) found that a dry mouth occurs commonly after I.V. injection of disopyramide which is used in cardiac arrhythmias.

- Tricyclic antidepressants e.g. imipramine (Tofranil) have anticholinergic action, so it lead to dry mouth. (Lourence 1973).

2. Stomatitis :

On mucous membranes 2 types of local reactions may in general be elicited : primary irritation caused by toxic materials and contact allergic reactions. The absence of a keratine layer, of hair follicles, sebaceous

and sweat glands modifies the effect of the reactions. The presence of saliva and of an abundant mucosal vascularization tend to favour rapid absorption of the allergic or toxic compound.

The oral mucous membrane is more resistant to the effect of primary irritants. (Meyler, 1972 - 1975).

- Glink, (1974)found that Aspirin held in the mouth used in the form of a rinse or placed in mucobuccal folds opposite teeth produces a chemical burn, this is due to local irritating effects.

- Lourence (1973) said that tetracycline lead to disorders of epithelial surface, perhaps partly due to Vit.B. complex deficiency and partly to mild superinfection with yeasts or moulds lead to sore mouth and throat.

- Lourence P. Garrod (1973) found that soreness of the mouth is fairly common if a course of treatment by chloramphenicol exceeds one week. It is attributable to depression of the normal flora by the antibiotic in the saliva and consequent overgrowth of candida albicans. Mild cases show little change, but in the more severe there is frank stomatitus, it is possible that vitamin B. deficiency or even a direct action of the antibiotic on the epithelium of the tongue leads to atrophic changes. Also (Meyler 1972 - 1975) said that : chloramphenicol

produces 2 distinct types of bone marrow damage :

a) An immediate type of reaction which is dose dependent and causes a reversible suppression of the formation of erythrocytes, thrombocytes and granulocytes and,

b) A delayed type of reaction which occurs less frequently but in most cases has the nature of an irreversible pancytopenia and is associated with a very high mortality. Granulocytopenia causing ulceration of the mouth and throat.

- According to Meyler 1972-1975, Penicillamine induced stomatitis by various mechanism :

1) An allergic reactions in association with a generalized allergic eruption.

2) Increase friability of the epithelium due to the production of poor collagen.

3) A pemphigus like disorder caused by production of antibodies against the intracellular substance.

4) Pyridoxine deficiency, which is more likely where L. penicillamine containing compound has been given.

5) Agranulocytosis may be associated with necrotic ulcers.

- Antineoplastic drugs : e.g. Nitrogen mustards, 5. fluorouracil, 6. mercaptopurine, Methotrexate, and L. asparaginase. All these drugs damage nuclei and cytoplasm of normal as well as neoplastic cells. Interference with maturation of cells results in regression of solid tumors but also gives rise to side effects. Also 5. fluorouracil inhibits the synthesis of DNA and to a lesser extent R.N.A. This antimitotic action is responsible for the side effects as stomatitis (Cuneri A.R. 1958).

- Strouthidis, T.M., Mankikar, G.D. and Irvine, R.E. (1972) treated seventy six incontinent patients with emepronium bromide using the dose recommended by the manufactures - 100 mg. three times a day and 200 mg at night. In thirteen patients (17%) four men, nine women, mouth ulcers developed. All the patients were mentally impaired. The lesions occurred in the first 3 weeks of treatment. They were unilateral, starting as bullae, later ulcerating and involving the tongue and adjoining mucosa, and occasionally the lower lip. The ulcers healed when the drug was withdrown, and when one patient was exposed to the drug again ulceration of the mouth recurred. The mechanism appears to be local irritation, though dryness of the moth may be an additional factor. It appeared that the ulcer developed in those patients who held the tablets in the mouth. The