THE GENERAL PHYSICAL AND CARDIOGRAPHIC TOXIC BRUNT OF AMPHETAMINE HYPERTHYROID INTERACTION

THESIS

Submitted In Partial Fulfillment
Of the Master Degree In
CLINICAL TOXICOLOGY

BY

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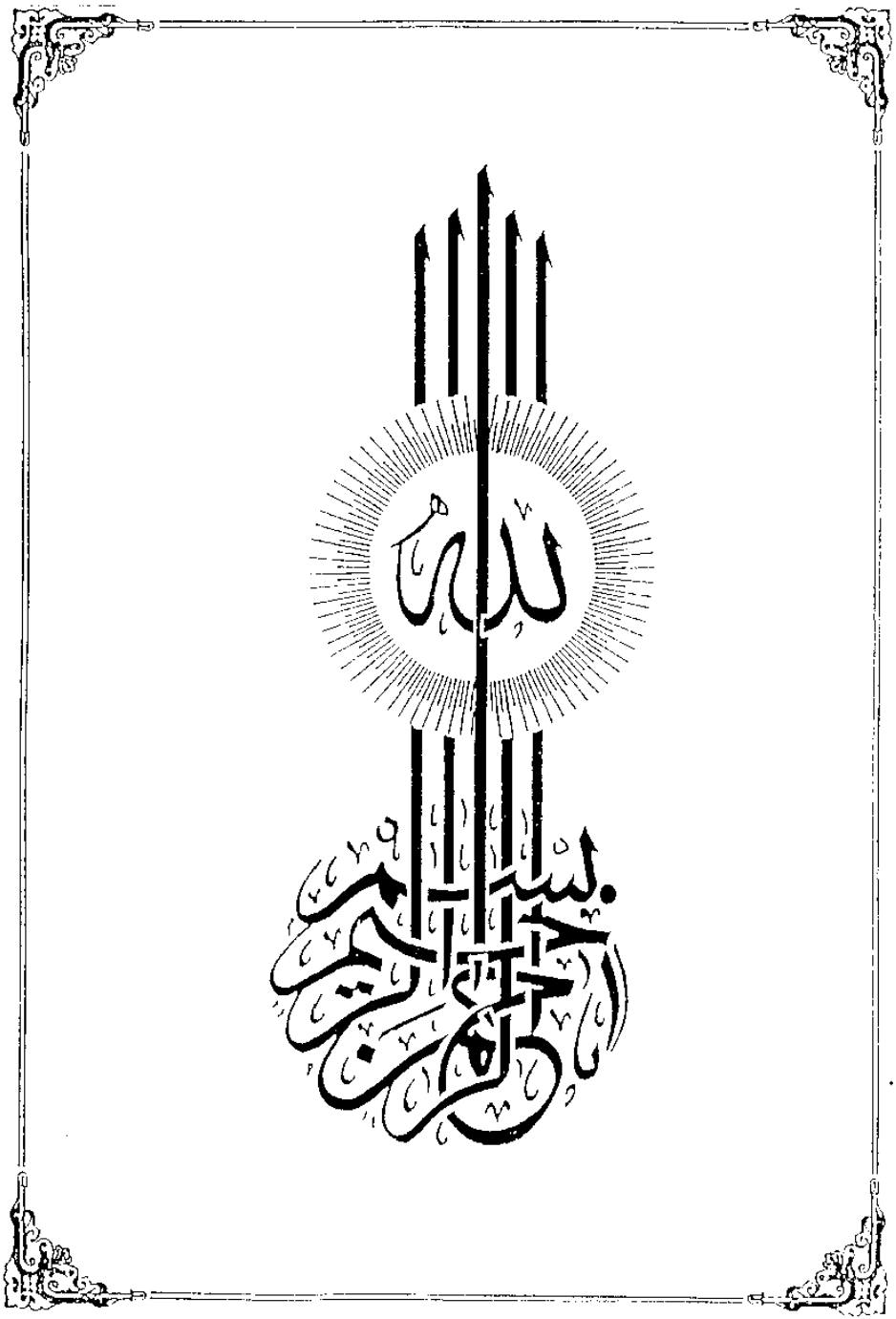


C O N T E N T S

OBJECTIVE

Owing to the growing abuse of amphetamine as pop-pills and anorexigenic agents, this thesis is constructed firstly to reveal the toxic hazards of this drug. Secondly the toxic effects of increased thyroid hormone will be looked for because it is still used for weight reduction. The third and main objective will be the experimental disclosure of some parameters of the combined toxic effects of thyroxine and amphetamine.

PROLOGUE

One of the most common diseases since ancient times is obesity. A caricature stone engraving of a fat Ancient Egyptian is documented. Ridicule of robust or fat individuals is a common behavioural mistake up to this day. Such a wrong social attitude places the obese individual into a dilemma of misery and even self pity, which may lead him to more indulgence in food.

Diet-regimens are the best measure for weight reduction specially when accompanied by moderate exercises. Such diets are hard to follow by the basically glutton. This inactive and chewing oriented individual usually tries to find a more convenient, although dangerous, method for weight reduction. Accordingly he resorts to the use of "slimming" drugs through self prescription or unauthorized non-medical advice. The two main drugs are those which increase satiety by central anorexigenesis; or speed fat "burning" by hypermetabolism. The parent drug of the anorexigenic series is amphetamine sulphate which, unfortunately, is still in manufacture. The most efficient hypermetabolic agent is l-thyroxine sodium. The obese human still seeks the "decrease in his appetite" by anorexigenesis and "increase in his fat burning" by hypermetabolism; accordingly he is fighting a small

fire by pouring benzene. For the sake of a supposedly "handsome or smart" looks he pushes toxicity of such drugs into his body systems. A great victory in the medical practice is conquering obesity without resorting to potentially toxic agents.

AMPHETAMINE

HISTORICAL SYNOPSIS

The pressor effects of amphetamine were first described by Piness and associates (1930). Alles (1933) observed its bronchodilator, respiratory stimulant, and analeptic actions and comparing it with epinephrine found that its cardiovascular effects to be of longer duration but of lower potency.

The central stimulant effects of amphetamine were first used clinically by Prinzmetal and Bloomberg (1935) to treat narcolepsy, and have since been employed in obesity, fatigue, parkinsonism and poisoning by CNS depressants.

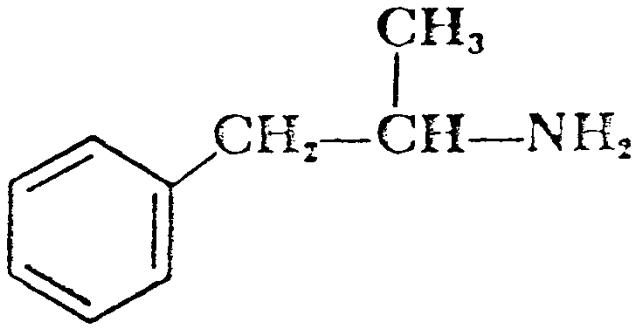
Amphetamine has been used for many years as an adjunct to phenobarbital in the treatment of epilepsy to counteract the ataxia and drowsiness produced by barbiturates (Cohn & Myerson, 1938). D-Amphetamine has been shown to potentiate the anticonvulsant activity of diphenyl hydantoin and phenobarbital. However, Jurna and Regelhy in 1968, found that amphetamine lowered the threshold to electroshock seizures in rats.

CHEMISTRY OF AMPHETAMINE

Chemical Structure:

B-phenylethylamine can be viewed as the parent compound of sympathomimetic amines. The amphetamines are regarded as sympathomimetic amines because of the similarity of structure and action to catecholamines (Smith, 1970). The structure permits the substitution on the aromatic ring, the ∝-and B-carbon atoms, and the terminal aminogroup to yield a great variety of compounds having sympathomimetic activity.

Amphetamine is a B-phenylisopropylamine lacking both OH groups on the benzene ring, increasing the effectiveness and the duration of action. In addition substitution on the ∝-carbon atom by ∝-methyl group prolongs greatly the duration of action, as its oxidation by monoamine oxidase is blocked (Weiner, 1980).



Amphetamine

B-Phenyl isopropylamine (Amphetamine)
(Goth, 1984).

Preparation and Administration

Amphetamine is available in 5 and 10 mg tablets and 15-mg slow release capsules. The d-isomer is available as Dextro-amphetamine phosphate, in 5-mg tablets, and as Dextro-amphetamine sulphate, U.S.P. (Dexdrine), in 5-and 10-mg tablets, in an official elixir (1 mg/ml), as an injection (20 mg/ml), and 5-, 10-, 15 mg slow release capsules (Weiner, 1980).

Maxiton: Dexamphetamine tartrate (Reynolds & Prasad, 1982).

PHARMACOKINETICS OF AMPHETAMINE

I . Absorption:

Amphetamine is effective by all routes, and acts for several hours. This is due to its resistance to the inactivating enzymes of the liver and other tissues (Goodman & Gilman, 1980). Amphetamines administered orally are absorbed mainly from the small intestine and reach their peak-blood levels after about 2 hours while chloro-amphetamine is more slowly absorbed and its peak blood level is reached after about 4 hours (Brookes, 1977).

II . Distribution & Metabolic Detoxification

After reaching the blood, it crosses the blood brain barrier easily, this is in part account for its relatively powerful CNS activity. In the brain, high level of the drug is detected in the grey matter at short intervals after administration, while at longer intervals distribution between white and grey matter becomes more uniform. In peripheral tissues the greatest concentration of the drug was seen in the highly vascularized organs (Latini, et al., 1977).

Amphetamine is metabolized via several pathways, including p-hydroxylation, N-demethylation, deamination

and conjugation in the liver, take part in its disposal. The main metabolite is phenylacetone, another minor metabolite, p-hydroxyamphetamine is taken by adrenergic nerves and changed to p-hydroxyncrephedrine stored in vesicles, thus forming a false transmitter (Goth,1984).

III. Elimination

A considerable part is excreted in the urine, while non appears in the faeces (Dring et al., 1966). Almost one third is eliminated unchanged in man. The rest about two thirds" of the d-amphetamine is hydrolysed in the para position (Beckett, 1969 and Vree, et al.,1971).

Its urinary excretion is affected by urinary pH. The percentage of non-ionized part of amphetamine increases in alkaline urine and its reabsorption by renal tubules is increased. If urine is acidic excretion may reach 80% (Beckett & Rowland, 1965). Hence the action of amphetamine is prolonged by taking sodium bicarbonate (Louis, 1986). The acidification of urine by the administration of ammonium chloride is a logical procedure in the treatment of amphetamine poisoning. After a single large dose, amphetamine is slowly excreted over 5-7 days suggesting that cumulative effects might occur with repeated administration (Connel, 1958).

PHARMACODYNAMICS OF AMPHETAMINE

Anorexigenic Effects:

Amphetamine has been widely used in weight reduction, although the wisdom of this use is at best questionable. Weight loss in obese humans treated with amphetamine is due to reduced-food intake and only in small measure to increased metabolism (Blundell and Leshem, 1973).

It was reported that its site of action is central and is probably in the lateral hypothalamic feeding centre, i.e. Satiety Centre; Injection of amphetamine into this area suppresses food intake. In man, some drug-induced loss of acuity of taste and smell has been described, together with increased physical activity may contribute to the loss of weight (Tecce & Cole, 1974). In dogs, the effect is powerful and may lead to complete starvation if amphetamine is given daily, one hour before meal. This effect is much less in man, and tolerance to acceptable doses develops rapidly and weight loss ceases in 6-8 weeks, as recorded by Meyers et al., (1976), unless diet is restricted. Weight loss is usually transient (OBrien & Woody, 1982).