Interaction Between Phenylpropanolamine and Acetaminophen

Thesis
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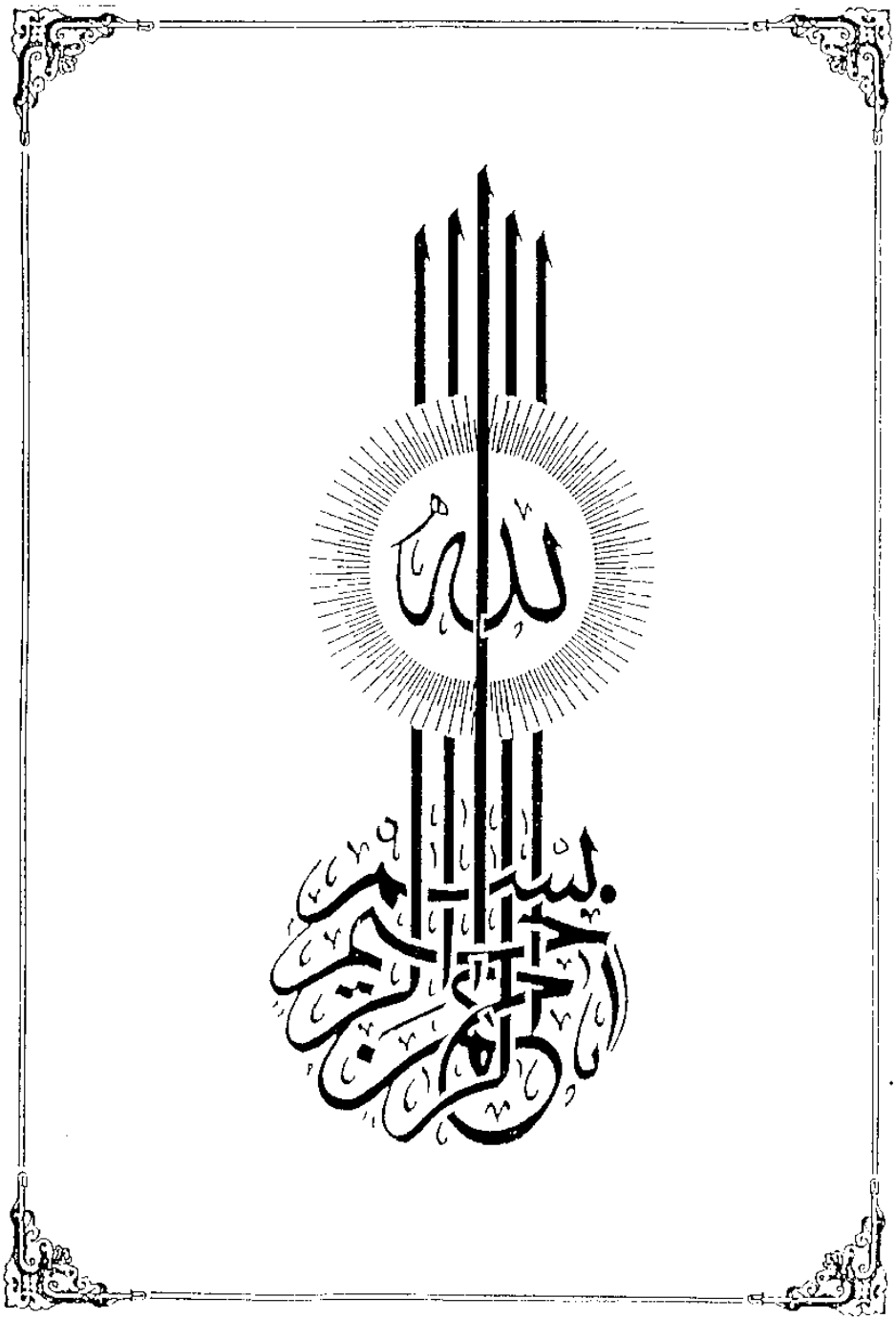

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Combination of drugs are used for many reasons. They may be necessary for a patient who has more than one disease or if different aspects of the same disease require different treatment.

Acetaminophen and phenylpropanolamine are a common combination in cold remedies used as an over-the-counter (OTC) medication. The misuse or abuse of OTC products may actually produce significant medical complications. The clinicians must be aware of these products and their formulations to avoid drug related problems in their patients (Katzung, 1992).

Ingestion of large amounts of acetaminophen causes serious hepatic toxicity. Phenylpropanolamine, commonly used as a nasal decongestant causes potentiation of this hepatotoxicity (James et al., 1993).

OTC products should be used with caution in selected patients because they may exacerbate existing medical problems or interact with prescription medications the patient is taking (Katzung, 1992).

Hepatic patient should avoid acetaminophen containing OTC products.

AIM OF THE WORK

The aim of this work is to throw the light on drug interaction between phenylpropanolamine and acetaminophen.

REVIEW OF LITERATURE

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PHENYLPROPANOLAMINE

HISTORY

In December 1978, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products of the FDA concluded that phenylpropanolamine (PPA), which had been permitted since 1975 in nasal decongestants, was generally safe and effective for weight control for up to 12 weeks in a daily dosage of not more than 100mg in divided doses. The panel increased the maximum daily dosage for PPA to 150 mg in January in 1979 (Ellenhorn and Barceloux, 1988).

The FDA has not approved the increased dosage. PPA containing products were rushed to market with higher than allowable amounts per dose (BLum, 1981).

At the same time and probably as a result of the sudden PPA usage, the FDA began to take measures to remove from the market amphetamines used for the management of obesity (Gunby, 1979).

Thus PPA, a synthetic sympathomimetic compound with action similar to ephedrine and the amphetamines and with the same potential adverse effects, is being heavily promoted for the same

indication unacceptable to the FDA for its chemical relative, amphetamine (Ellenhorn and Barceloux, 1988).

Serious adverse effects of PPA in therapeutic doses and in overdose in both children and adults have become apparent within the past few years (Bale et al., 1984 and Mueller, 1983).

CHEMISTRY

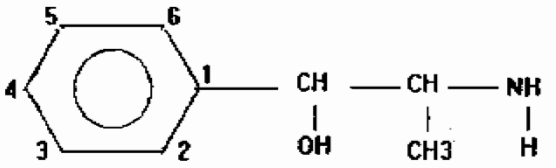


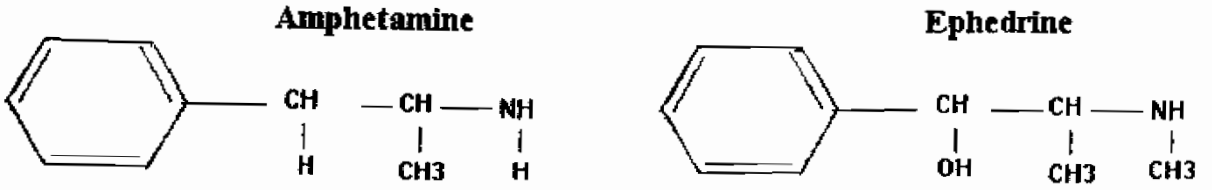
Fig (1): Chemical structure of Phenylpropanolamine (Goodman et al., 1991).

PHARMACOLOGICAL PROPERTIES

Phenylpropanolamine (PPA) occurs as a white crystalline powder having a slight aromatic odour and a pka of 9 (Ellenhorn and Barceloux, 1988).

It is soluble in 2.5 parts of water and in 9 parts of ethanol (96%) and is practically insoluble in chloroform and in ether (Caws et el., 1988).

It is a synthetic sympathomimetic drug structurally related to ephedrine and amphetamine. It shares the pharmacological properties of ephedrine and is approximately equal in potency except that it causes less central nervous system stimulation (Goodman et al., 1991).



Fig(2) Chemical structure of amphetamine and ephedrine (Ellenhorn and Barceloux, 1988).

PPA is primarily an indirect α-adrenergic agonist releasing norepinephrine at postganglionic sympathetic nerve terminals. It also has direct α-agonist properties and has a lesser degree of β-agonist activity. Its efficacy as an appetite suppressant may result from increased norepinephrine concentrations in brain areas but this has not been established (Ekins & Spoerke, 1983).

It causes increase in blood pressure due to vasoconstriction (minor) and cardiac stimulation (major). (Olin et al., 1993).

The elevation in blood pressure is usually associated with reflex bradycardia mediated by baroreceptors and this can result in postural hypotension. An antihistamine or anticholinergic may block this effect. This is largely due to the fact that PPA has α-agonist activity but very little β-agonist activity. Nasal decongestion is a result of direct alpha vasoconstriction of the mucosal blood vessels (Laurence and Benett, 1985).

PHARMACOKINETICS

ABSORPTION

Oral therapeutic doses of phenylpropanolamine are widely absorbed from the gastrointestinal tract, with maximal therapeutic effect in 1 to 3 hours (Horowitz et al., 1980).

Therapeutic serum conc. are 60 to 200 mg/ml (Olin et al., 1993).

Nasal decongestion may occur within 30 minutes after 25 mg PPA is administered orally. In overdose, the peak reaction is usually seen within 2 to 3 hours after ingestion (Pentel et al., 1982 & Saltzman et al., 1983).

DISTRIBUTION

Distribution occurs widely into many tissues including the cerebrospinal fluid and brain as shown by animal studies. No studies in man are available (Ellenborn and Barceloux, 1988).

METABOLISM

Small amounts of the drug are slowly metabolized in the liver to an active hydroxylated metabolite (James et al., 1993).

ELIMINATION

PPA is a weak base and is eliminated most rapidly in an acid urine. In an acid urine, the elimination half life is 2.7 to 3.4 hours (Pentel, 1984).

In alkaline urine, the half life has not been established. 80% to 90% of PPA is eliminated unchanged in urine. Since urine PH is usually in the range of 5.5 to 7, acidification procedures are usually unnecessary (Ellenborn and Barceloux, 1988).

THERAPEUTIC USES

1) NASAL DECONGESTION

α-adrenergic agonist phenylpropanolamine is used extensively as nasal derongestant in patients with allergic or vasomotor rhinitis and in acute rhinitis in patients with upper respiratory infections (Empey and Medder, 1981).

These drugs decrease resistance to airflow by decreasing the volume of the nasal mucosa. This may occur by activation of α-adrenergic receptors in the venous vessels found in the nasal tissues that have erectile characteristics (Cole et al., 1983).

The receptors that mediate this effect appear to be α1-adrenergic receptors. Contraction of arterioles that supply nutrition to the nasal mucosa is mdiated by α2-receptors (Anderson and Bende, 1984).

Intense constriction of these vessels may cause structural damage of the mucosa (De Bernadis et al., 1987).

Rebound congestion and worsening of symptoms often occur from the regular use of nasal sprays for more than 3-4 days (Katsung, 1992).

Although mechnisms are uncertain, possibilities include receptor desensitization and damage to the mucosa. Agonists that are selective for $\alpha 1$ receptors may be less likely to induce mucosal damage (De Bernadis et al., 1987).

A variety of compounds are available for topical use in patients with rhinitis. Topical decongestants are particularly useful in acute rhinitis because of their more selective site of action, but they are prone to be used excessively by patients, leading to rebound congestion. Oral decongestants are much less likely to cause rebound congestion but carry greater risk of inducing adverse systemic effects (Laurence and Bennett, 1985).

2) WEIGHT REDUCTION

Obesity arises as a consequence of positive caloric balance. PPA can be used as an anorexiant for the treatment of exogenous obesity as a short-term (8-12 weeks) therapy in a regimen of weight reduction based on caloric restriction. It is given alone or in combination with caffeine, vitamins, methylcellulose, fructose, lecithin and grapefruit extract (Weintraub et al., 1986).