The Teratogenic effect Induced by Some Drugs Acting on the CNS During Gestation

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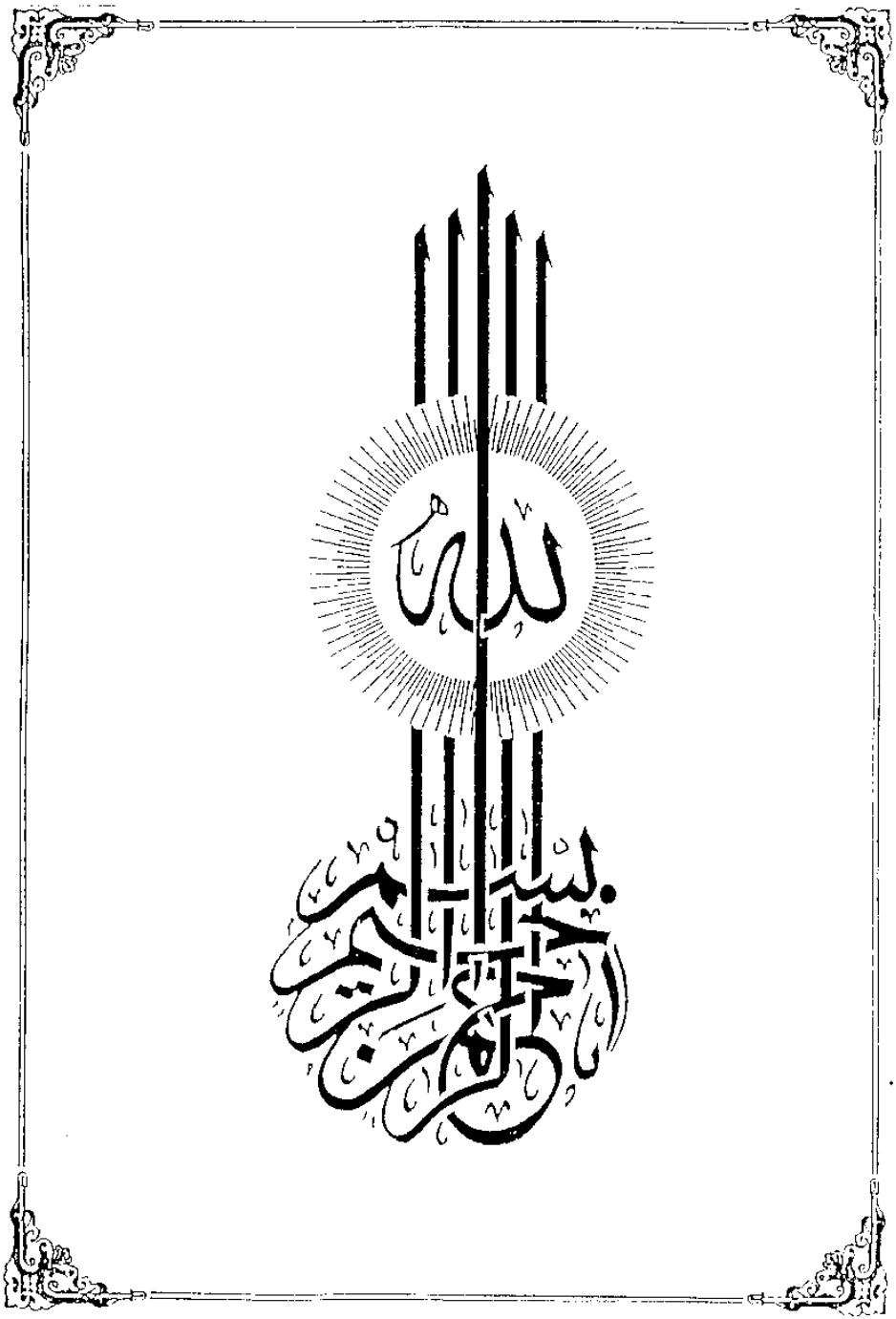

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AIM OF WORK

INTRODUCTION AND AIM OF THE WORK

Abuse of drugs has increased dramatically all-over the world during the past decade. The wide spread misuse of sedatives (e.g diazepam) and abuse of stimulants (e.g cocaine), especially among the middle age group, has led to the growing concern about the effects of these drugs on the exposed fetuses. It has also been reported that those addicts abuse more than one drug at the same time to depress the manifestations or physical dependence of another drug.

Since the literature available on the teratogenic effect of diazepam and cocaine is sparse, this study has been conducted to evaluate the teratogenic potential of diazepam, cocaine and their combination. The route of administration of cocaine adopted in this study was the intravenous route because it is one of the common routes of administration among drug addicts and the closest to the inhalation route. While diazepam has been given by gavage, simulating the route by which it is commonly used by addicts.

In this teratologic study all treated dams of the different groups will be observed daily for their gross appearance and behavior to insure that the maternal dose has been far below the toxic level. Half the litter of each dam will be processed for visceral examination while the other half will be cleared and stained for skeletal examination.

Cocaine is considered by many investigators to be a powerful hepatotoxin. However, the hepatotoxic potential of cocaine has not been evaluated at the fetal level if the mother has been exposed to cocaine during pregnancy. In an attempt to find any relationship between phenotypic anomalies and alterations in the liver cells, two fetal livers from the litters of each treatment regimen will be fixed and processed for ultrastructural evaluation. In addition, livers of dams will be also processed for light and electron microscopic studies.

In relation to these hepatic ultrastructural studies, it has been suggested to investigate the activity of some enzymes pertinent to the liver function such as glutamic oxaloacetic- and glutamic pyruvic-transaminase. Moreover, the effect of cocaine and diazepam on the endoplasmic reticulum function will be evaluated through microsomal separation and the estimation of the cytochrome P-450 activity. The protective role of reduced glutathione against hepatic damage will be also assessed by estimating the level of reduced glutathione under different treatment regimens.

Since hepatotoxicity studies on this particular strain of CF-1 mice has not yet been explored, particularly in regard to exposing both sexes to the administration of cocaine, it has been planned to carry out some comparative preliminary observations on the males of the CF-1 strain.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Drug Abuse:

As far back as recorded history, every society has used drugs that produced effects on mood, thoughts and feelings. Moreover, there were always few individuals who digressed from custom with respect to the time, the amount and the situation in which these drugs were to be used.

Drug abuse refers to the use usually by self administration of any drug in the manner that deviates from the approved medical or social pattern within a given culture. The term "abuse" is different not only from culture to culture but also from time to time and from one situation to another within the same culture. Many factors determine the acceptance of a particular drug, the social attitudes and the individual access as well as the laws of any given country. In general, when the use of a drug is widely accepted the number of users tends to be large and their personal characteristics are quite diverse. Thus, abuse of drugs is as old as civilization itself (Jaffe, 1985).

Non medical drug use:

The assessment of the non-medical use of licit drugs presents even more problems. These substances have legitimate medical uses, hence their misuse is far less visible and much more difficult to assess. Since we still lack the important

ratios which would enable us to estimate the specific abuse rates per drug category in the population. For example, we do not know the rate at which heroin users get non-transfusion serum hepatitis B ; if we did, we could have back estimated the number of heroin users in the reporting areas (Lipton, Stephens, Kaestner, Diamond, and Spielman, 1975).

One of the hazards in the use of drugs altering mood and feeling is that some individuals develop dependence on the drug. They continue to take it in the absence of medical indications, often despite adverse social and medical consequences. The intensity of this "need" or dependence might vary from a mild desire to a craving or compulsion to the use of the drug i.e addiction.

One of the common facts that is shared among the addicts is the variety of drugs usage by the same individual which, pharmacologically related, more or less give the same or depress the manifestations of physical dependence of the first drug, this is called "Cross-dependence" which is found, not only among most sedative-hypnotics, but also with alcohol, barbiturates, amphetamine and cocaine since many cocaine users simultaneously consume large amount of barbiturate, alcohol or sedatives (Jaffe, 1985).

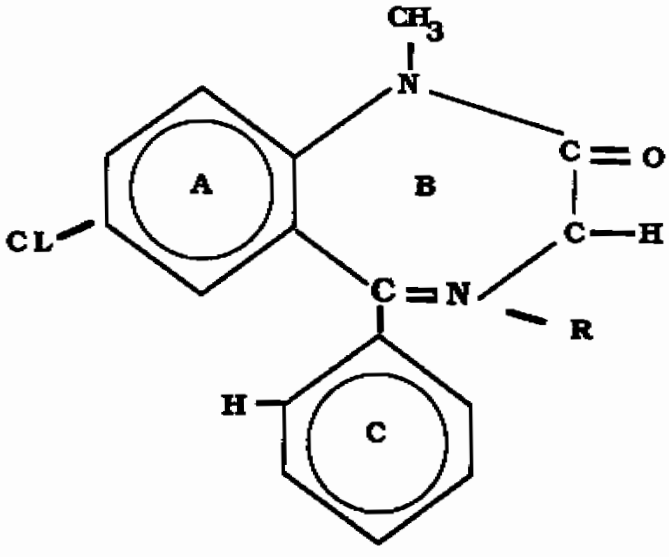
SEDATIVE AND HYPNOTIC DRUGS:

The definition of a sedative is a drug that decreases activity, moderates excitement and calms the recipient. While

a hypnotic is a drug that produces drowsiness and facilitates the onset and maintenance of sleep that resembles natural sleep in its encephalographic characteristics.

Barbital was introduced in 1903 and phenobarbital in 1912. Their success spawned the synthesis and testing of over 2500 barbiturates of which approximately 50 were distributed commercially. Chloropromazine and meprobamte were then introduced in the early 1950 with their taming effect on animals, and the development of increasingly sophisticated methods for the evaluation of the behavioral effects of drugs. Benzodiazepines were then selected for their high anxiolytic potential and low potency as general depressant of CNS function. Chlorodiazepoxide was the first of this group to be introduced and was followed by diazepam by Randall, Heise, Schallek, Bagdon, Banziger, Boris, Moe, and Abrams, (1961). Their extraordinary popularity in clinical medicine is largely due to their ability to relieve symptoms of anxiety with minimal interference with cognitive function or wakefulness mainly because of their remarkably low capacity to produce fatal CNS depression. The benzodiazepines has largely replaced the barbiturates as a sedative hypnotic drug. Among the 3000 benzodiazepines that have been synthesized over 120 have been tested for biological activity, and 25 are in clinical use in various parts of the world (Harvey, 1985). However,since the introduction of diazepam in the early 1960 it is still widely used for a large variety of indications.

A– DIAZEPAM CHEMISTRY:



Diazepam is formed from a benzene ring (A) fused to a seven-membered diazepine ring (B), it also contain a 5-aryl substituent ring (C). It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.74.

PHARMACOLOGICAL ACTIONS OF DIAZEPAM:

There is now reason to believe that a number of distinct mechanisms of actions contribute in varying degrees to the sedative hypnotic, muscle relaxant, anxiolytic and anticonvulsant effects of diazepam; these mechanisms are currently under intense investigation. Randall, *et al.* (1961) had shown that diazepam depress the limbic system, without causing cortical depression. Their tranquillizing effect were thought to be due to an action on the amygdala, the part of

the limbic system which is the relay area for the expression of emotions. This was shown to reduce the aggression more than activity in monkeys. These effects were the basis for the employment of these drugs in psychiatric practice, particularly in anxiety states. Using cells from embryonic mouse spinal cord which were dissociated and grown for several months in culture it was shown that diazepam potentiated the inhibitory action of applied GABA (Macdonald, and Barker, 1978). Currently there is general agreement that most if not all of the actions of benzodiazepines are the result of potentiation of the neural inhibition that is mediated by gamma-aminobutyric acid (GABA).

PHARMACOKINETICS OF DIAZEPAM:

Cameron, (1971) showed that diazepam was rapidly absorbed from the gastrointestinal tract, and biotransformation occurred by n-demethylation and hydroxylation to yield oxazepam. Following the ingestion of 10 mg dose, 71% of the drug was excreted in the urine, and 10% in the feces. About 33% of the dosage was metabolized as oxazepam gloucoronide, 10% as conjugated n-demethylated metabolite and 10% as the conjugated 3- hydroxylated metabolite. Greenblat, Shader, and Abernethy, (1983) have reported that oral absorption from the gastrointestinal tract into the circulation is the limiting factor for the action of diazepam after a single oral dose rather than the much more rapid passage from the blood into the brain. They also stated

that hepatic biotransformation accounted for essentially all benzodiazepine clearance or elimination. The two principal pathways involved were either hepatic microsomal oxidation (N-dealkylation or aliphatic hydroxylation) or glucoronide conjugation. The duration of action of diazepam bears little relationship to the half life of the drug since its metabolites retain the pharmacological activity and are transformed more slowly than the parent compound (Harvey, 1985).

BENZODIAZEPINES ABUSE:

Although diazepam have a reputation for causing only a low incidence of abuse and dependence, the possibility of this adverse complication of chronic use must not be overlooked. The original contact of the drug might have been through a physician's prescription or illicit drug trade. In the medical patient, the development of the problem may be a gradual one beginning with prolonged use for insomnia or anxiety and progressing through increased dosage at night to a few capsules for sedation in the morning. It is well known that the dependence developing by these drugs is not obvious, since neither the patient nor the physician may recognize the presence of dependence over a period of months, both may assume that anxiety and insomnia that emerge when the drug is discontinued is a return of the original anxiety for which the patient started this medication (Smith, 1977; and Wesson, and Smith, 1977).

Mackinnon, and Parker, (1982) reported that the abusers of benzodiazepines may ingest several hundred milligrams of diazepam or its equivalent every day.

In 1982, 19% of young adults reported non-medical use of sedatives with 2.6% describing some use in the preceding month. About 15% indicated some experience with non-medical use of tranquilizers. The incidence was relatively stable over the preceding 5 years (Miller, Cisin, Gardner- Keaton, Harrell, Wirtz, Abelson, and Fishburne, 1983). The incidence and prevalence of non-medical and compulsive use of benzodiazepines and barbiturate are exceeding greatly that of the opioids.

In general the subjective effects of sedatives and anxiolytic agents are similar but not identical to those of alcohol, and the effects vary considerably with the dose, the situation, and the personality of the user. The overwhelming preponderance of reported cases involved diazepam used to treat anxiety often in combination with other abused drugs. Opioid users frequently take barbiturates and benzodiazepines to augment the effects of weak illicit heroin or to produce psychological effects when they become tolerant to the prescribed opioids. Many heroin users and patients maintained on methadone are physically dependent on both opioids and sedatives. Some alcoholics use these agents to relieve the alcohol withdrawal syndrome or to produce intoxication devoid