CHAPTER - II

REVIEW OF LITERATURE
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Caffeine, analgin and contramal are widely used as an analgesic, antipyretic and even as antiinflammatory drugs. However, their uncontrolled use cause several unwanted effects like CNS disturbances, acid-base and electrolyte imbalance of the body (Flower et al., 1985). Hepatotoxicity and hyperglycemic effect of caffeine has been studied by Chatterjee and Kaveeshwar (1979), after administration of caffeine citrate, at 10 mg/kg body weight.

Caffeine has also been shown to increase the intracellular calcium by promoting its release from the
endoplasmic reticulum and by facilitating its influx through "slow channels" in the cell membrane (Itoh et al., 1977).

Saxena et al. (1984) recorded decrease in thymus weight in rats along with alteration in its histological structure. They have also reported increase in body weight in rats after 30 days of administration of caffeine. Besides, following chronic exposure of rats to caffeine, many workers suggested the association of hypertrophy of adrenal glands, histopathological changes in various organs and cardiovascular diseases with caffeine (Saxena et al., 1984; Agarwal, 1995; Devasagayam and Kesavan, 1996).

Singh et al. (1984) studied the effect of caffeine on bone marrow cells of mice. They fed caffeine to the albino mice at a dose of (0.2, 0.1 or 0.05 x LD 50) for seven consecutive days and observed a dose dependent reduction in the viability of cells both under in vivo and in vitro conditions. Further, peripheral blood exhibited no changes in RBC counts and an increase in granulocyte number was observed with higher doses of caffeine.
Caffeine is generally known to increase the strength of contraction in heart muscles. The potentiation of twitch tension is thought to be mediated primarily by an increase in sarcoplasmic Ca\(^{++}\) concentration, as a result of enhanced Ca\(^{++}\) release from sarcoplasmic reticulum (Nayler and Hasker, 1966; Weber and Herz, 1968; Thorpe, 1973) or increased influx of Ca\(^{++}\) across the sarcolema (Blinks et al., 1972).

The effect of caffeine on isometric concentration of right - ventricular strips during the postnatal development of the rat heart was studied by Matti (1984). He reported that caffeine had a positive inotropic effect on ventricular strips of 3-15 days old rats but a negative inotropic effect on the muscles of rats older than 22 days.

In one study, decreased exploratory behaviour in mice was seen by Gywali et al., (1991). Phillips and Wu (1982) have suggested that at low doses, caffeine excite central neurons releasing adenosine in sufficient quantities to exert an ongoing modulation of synaptic transmission in the intact brain.
The possible physico-chemical and molecular mechanisms of caffeine action are reviewed by Devasagayam and Kesavan (1996). According to them caffeine, a major constituent of coffee and other beverages have significant abilities to scavenge highly reactive free radicals and excited states of oxygen and to protect crucial biological molecules against these species.

Considerable evidences for impairment of immunocompetence caused by high doses of caffeine are available (Singh et al., 1984; Saxena et al., 1984; Dews, 1984; Ajarem and Ahmad et al., 1996). It is well documented that high doses of caffeine can cause acute structural teratogenesis in animals (Legator and Zimmering, 1979; Yanai, 1984). The exposure of pregnant rodents during early embryogenesis may result in many developmental, behavioural and biochemical changes in their off-springs (West et al., 1986; Pauard et al., 1987; Ajarem and Ahmad, 1991; Nehling et al., 1992). Ajarem and Brain (1993) have demonstrated that the prenatal exposure of mice to caffeine has produced a lasting influence on the behaviour, as well as body weight gain of cross-fostered offsprings via a direct in utero action. Human studies have also indicated an
association between foetal loss, foetal growth, retardation and foetal low birth weight due to excessive coffee intake during pregnancy (Weathersbee and Lodge, 1977; Martin and Bracken, 1987).

The possible relationship between exposure to coffee during pregnancy and the teratopharmacological effects on the developing neonates was evaluated in the albino mice by Ajarem and Ahmad (1996).

Studies related to tissue distribution of caffeine and its metabolism in rodents have showed that caffeine appeared in all tissues in proportion to tissue water, including lymphoid organs. Its half life in plasma and tissue, varied with doses (Gilbert et al., 1976).

Riesselmann et al. (1999) have recently observed fatal caffeine intoxication and concluded that caffeine concentrations in plasma above 15 mg/l can cause toxic symptoms while values above 80 mg/l are considered to be comatose - fatal. They were able to detect fatal caffeine intoxications twice during 1998 - 99 in toxicological analysis.
Pelissier et al. (1999) studied caffeine induced modifications of heart rate, temperature, motor activity, and circadian rhythms in rats. Their results indicated that caffeine did not suppress the circadian rhythmicity of heart rate, body temperature and motor activity. But caffeine significantly increased the measures and decreased the amplitudes of the three rhythms and also advanced the acrophases of temperature and activity, when compared to the control group.

Publications about fatal caffeine overdose are relatively rare. However, Riesselmann et al., (1999) were able to detect fatal caffeine intoxications with caffeine concentrations 200 mg/l in femoral blood. The consumption of caffeine during pregnancy increase the risk of spontaneous abortion, is controversial (Klebanoff et al., 1999). They used a biologic marker, serum paraxanthine, a metabolite of caffeine, to measure the dose of caffeine. In a nested case - control study, they measured serum paraxanthine in 591 women who had spontaneous abortions at less than 140 days gestation and in 2558 matched women from the same clinic who gave birth to live infants at 28 week's gestation or later. They concluded that
moderate consumption of caffeine is unlikely to increase the risk of spontaneous abortion. Greer et al. (1999) and Graham et al. (1999) investigated the metabolic influence of caffeine during short term, high intensity exercise. They found increased plasma epinephrine concentration due to caffeine consumption. However, there was no indication of increased anaerobic metabolism after caffeine ingestion.

As early as 1899, it was claimed that at least part of the antiinflammatory action of aspirin like drugs was due to their central action. A few years later, it was reported that morphine could attenuate inflammation and it was postulated that inhibition of pain could decrease the inflammatory response (Bonta, 1978).

Altshelder et al. (1977) observed reduced urine volume and sodium excretion in rats after acute administration of aspirin.

Balasubramanian et al. (1979) studied the effect of acetyl salicylic acid on lung surfactant of rats. Rats fed 30 mg acetyl salicylic acid for 6 weeks showed a 25% decrease in the lung surface tension values (P < 0.001). Where as, rats injected
with 60 mg single dose of acetyl salicylate showed only 17 % ( P < 0.05 ) decrease.

The effect of acetyl salicylate on tolbutamide induced hypoglycaemia in normal and alloxan - induced diabetic rabbits was studied by Kumar et al. (1985). Single dose concurrent administration and seven days continued treatment with asprin ( acetyl salicylate ) enhanced tolbutamide - induced hypoglycemia.

Dhar and Farzen (1994) studied the mechanism of action of calcium channel antagonists ( nifedipine and diltazem ) in producing hyperglycemia. This hyperglycemic effect was found to be mainly due to reduced insulin release and its effect on overall glucose uptake by peripheral tissues.

The effect of aspro and saridon (analgesics) were assessed by Hardikarin et al. (2000) by evaluating lactate content in lymphocyte culture. They have observed increase in lactate content with decrease in pH. Gillies et al. (1986) have stated that analgesic mixtures are more effective to produce renal damage than single agents.
It has been experimentally shown that amino acid glutamine is analgesic (Jain and Khanna, 1981). Jain et al., (1988) studied the antiinflammatory and antinoceceptive effect of aspirin and L-glutamine combination, as measured by the carrageehan induced rat paw edema test, spong pellets test in rats and hot plate method in mice. Asprin has been reported to enhance spermatogenesis and fertility in mice (Balsubramanian, 1980), however, Ratnasooriys and Lionel (1984) have demonstrated that asprin temporarily suppresses the fertility of male rats when applied locally to the epididymis via a formulation made from medical grade silastic.

Paracetamol is widely used as analgesic and antipyretic drug. In case of poisoning with toxic doses of paracetamol, severe myocardial damage has been reported by Maclean et al. (1968). Acharya (1979) studied cardiac effects of paracetamol in human beings and found that paracetamol produced significant (P < 0.001) bradycardia with heart rate ranged from 4 to 14 beats per minute. Further, paracetamol could not produce any significant change in the diastolic blood pressure. However, there was a slight but insignificant reduction in the systolic blood pressure.
Bhounsule et al. (1990) have studied the comparison of four analgesics (ibuprofen, analgin, asprin and paracetamol) in post-episiotomy pain and ibuprofen was found to be the most effective analgesic in post-episiotomy pain followed by analgin, paracetamol and then asprin.

It has been reported that nifedipine causes hyperglycemia (Charles et al., 1981; Bhatnagar et al., 1984) and impairment of glucose tolerance in non-insulin dependent diabetics (Glugliano et al. 1980). Verapamil has also been reported to produce hyperglycemia in experimental animals (Shrivastava et al., 1990). Prolonged administration of nifedipine causes significant rise in blood sugar and reduces glucose tolerance in human volunteers (Shahani et al., 1990). However, it produced significant rise in liver glycogen without appreciable change in the heart and skeletal muscle.

Chinoy and Seethalakshmi (1978) have investigated the effects of analgesic drugs on the reproductive physiology of male albino rats and found that these drugs altered the metabolism of the testis and epididymis. Decrease in the organ weights and activities of some androgen dependent enzymes...
suggested that drugs inhibited the hypothalamo-pituitary-gonadal axis and thereby reduced testicular androgenesis. There are many reports which indicate the importance of protein denaturation as a cause of inflammation (Spector and Willoughby, 1962; Ischizaki, 1965; Grant et al., 1970). Bhaskar Rao et al. (1985) showed inhibition of heat produced denaturation of human serum albumin by antiinflammatory drugs and acetyl salicylic acid and ibuprofen.

Comparative evaluation of aspirin, ibuprofen, tometin and indomethacin was done on biochemical parameters like blood sugar, uric acid and on haematological parameters like clotting time, platelet count, and plasma fibrinogen content in rabbit by Sudha et al. (1987). Aspirin induced hyperglycemia, hypouricaemic effects and decreased coagulation time in rabbit. Zucker and Peterson (1970) demonstrated reduced release of platelet bound serotonin in human blood due to acetyl salicylic acid. Rishi et al. (1976) described increased fibrinolytic activity with aspirin.

*In vitro* effects of aspirin and paracetamol at the doses 200, 400, 600, 800 nmole/mg protein on ATPase activity
were studied in the cerebrum and cerebellum of human foetus covering the age range from 10 weeks to 32 weeks of gestation - by Sarker et al. (1989). Both aspirin and paracetamol inhibited Na\(^+\) K\(^+\) ATPase and Mg\(^{++}\) ATPase in a dose dependent manner and this affected the release and uptake of biogenic amines in CNS and hindered the maturation of human foetal brain. Chronic administration of salicylates during pregnancy have been reported to cause disorders in glucose metabolism and transmission processes leading to normal brain development and normal heart function (Mequeen, 1977). It has been demonstrated that aspirin can also cause malformation and resorption tissues in mice and rat embryo, if administered during pregnancy (Reynolds, 1983).

Johri et al., (1990) performed toxicity studies with an analgesic compound potassium embelate. They could not observe any adverse effect on the haematological parameters in albino mice. The parameters investigated were blood glucose, cholesterol, creatinine, uric acid, SGOT and SGPT.

Sufficient data is available on the action of acetyl salicylate regarding inhibition of platelet aggregation through
inhibition of cyclo oxygenase in blood vessel walls and other tissues, thereby inhibiting the synthesis of prostaglandins (Arfors et al., 1976; Rosenblum and Sabban, 1979 a, 1979 b; William et al. 1980 ).

Hepatotoxicity and renal toxicity of aspirin has been reported by several investigators (Clive and Staff, 1984; Das and Dasgupta, 1997). Aspirin induced CNS disturbances, acid-base and electrolyte imbalance were demonstrated by Flower et al., (1985).

Das and Dasgupta (1997) observed increased alkaline and acid phosphatase activities in the plasma of aspirin treated rats after 7 days of treatment. However, acid and alkaline phosphatase activities were found to be significantly decreased in liver and kidney of aspirin treated rats.

Antithrombotic effect of aspirin was first demonstrated by Lewis (1983) and he suggested the protective effect of aspirin against acute myocardial infarction and unstable angina.
Opioids act on the hypothalamus to inhibit the release of gonadotrophins releasing factor (GnRF) and corticotropin releasing factor (CRF) and thus decreasing circulating concentration of luteinising hormone (LH), follicle stimulating hormone (FSH), adreno corticotropic hormone (ACTH) and β-endorphin (Reisine and Pasternak, 1996).

Patil et al., (1998) studied the chronic effect of pethidine (synthetic opioid analgesic) on albino rats and found reduction in the weight of testis, its diameter and diameter of seminiferous tubules. They also reported regression in spermatogenesis and reduction in cauda epididymal sperm count. They attributed it to the non-availability of pituitary FSH during the entire experimental period.

Reports on the effect of pethidine, an opioid drug on reproduction are scanty. However, morphine, an another opioid has a well established tonic inhibitory influence on the neuroendocrine gonadal axis (Cicero et al., 1977; Ching, 1983; Cicero et al., 1985, Johnston et al., 1992;).

Bruni et al. (1977) studied the effects of naloxone, morphine and methionine enkephaline on serum prolactin,
luteinising hormone, follicle stimulating hormone and growth hormone, in albino rats and they concluded that an opioid had a tonic inhibitory influence on the neuroendocrine gonadal axis. However, Bustamante and Miranda (1991) have demonstrated the opioid system to be inresponsive to morphine in wistar rats.

Husselein et al. (1987) and Kaintz et al. (1992) observed no adverse effect on mother/ neonates after using tramadol 100 mg, (im) during labour. Prasertswat et al.(1985) reported satisfactory analgesia in 78 % cases and also reported insignificant difference with pethidine and morphine in analgesic potential. Tramadol shows some selectivity for opioid receptor (Raffa et al.,1992), but its only active metabolite O - dimethyl tramadol ( M1 ) shows higher affinity for this receptor ( Hennies et al.,1988). However, this metabolite was not found to contribute to the analgesic effect of a single dose of 100mg tramadol orally ( Lee et al. , 1993 ).

Tramadol has been reported to produce dose-released antinociception in mouse abdominal constriction, hot plate and tail flick tests ( Raffa et al. , 1992; Rhoda et al.,1993 ). In previous years, the pharmacology of opioids in various animal
models of experimental convulsions has been extensively investigated (Cowan et al., 1979; Frenk, 1983). Both pro- and anticonvulsant actions of morphine, a receptor agonist have been demonstrated (Frenk, 1983). Workers have reported, no consistent effects of classic Kappa agonists such as ethylketocyclazocine and ketocyclazocine in fluoroethyl seizure threshold test (Cowan et al., 1979). However, other studies pointed out an anticonvulsant effect in electroshock seizure model with drugs having either kappa or mixed mu and kappa agonistic activity (Czu-czwar and Frey, 1986; Fisher et al., 1993; Ray et al., 1993; and Monocha et al., 1998). In the recent past Monocha et al. (1998) have studied the anticonvulsant effect of tramadol against maximal electroshock seizure in mice.

Opioidergic inhibition of LH secretion may influence the rate of sexual maturation in male rats and a decline in opioidergic suppression of LH secretion may precede maturity (Bhanot and Wilkinson, 1983; Zagon and McLaughlin, 1984; Rawlings et al. 1991).

Kalra and Kalra (1983) have proposed that endogenous opioid peptides modulate GnRF secretion via
adrenergic neurons and that ovarian steroids influence the degree of endogenous opioid peptide (EOP) tone exerted upon this system. EOP exert tonic inhibition of LH secretion in sexually mature pigs (Barb et al., 1985; 1986), in rats (Kalra and Kalra, 1983) and sheep (Malven, 1986). Inhibition of gonadotrophin release in males and females of different species and increase in plasma LH concentrations after injections of opioid antagonists are also interpreted by Bruni, et al. (1977); Barb, et al. 1986; Lincoln et al. (1987); Newton et al., (1988); Mann and Bridges (1992); Evans et al. (1993); Aurich, et al. (1994); Smart et al. (1994); Hopewood et al. (1998); Rensis et al. (1998) as evidence of tonic inhibition of LH secretion by opioid system.

The modulatory role of \( \gamma \)-amino butyric acid (GABA), benzodiazepine Cl\(^-\) channel, neuronal Ca\(^{++}\) channels, N-Methyl-D-Aspartate (NMDA) and mitochondrial dizepam binding inhibitor receptors in the neurosteroid induced attenuation of opioid tolerance and dependence is investigated by several authors (Krueger and Popadopoulos, 1992; Majewska, 1992; Kulkarni and Reddy, 1995; French-Mullen et al., 1994; Irwin et al., 1992; Monnet et al., 1995; Frye, 1995; Reddy and Kulkarni, 1997a,1997b,1997c; 1998). The results of above
investigations indicated a role of dihydropyridine sensitive Ca^{++} channels in the action of neurosteroids and mitochondrial diazepam binding receptors in the 4Li-chlordizepam on the development of tolerance and dependence on morphine opioid.

Sreenivasan and Vijayan (1996) have demonstrated that opiates and opioid peptides influenced testicular metabolism, reducing LDH activity, which is a key enzyme in the metabolic process in the testis as lactate and pyruvates are the metabolites secreted by the sertoli cells which in turn are utilized in the maturation of spermatocytes and spermatids.

Tolerance to morphine analgesia was seen in diabetes by Naga Rani et al. (1996). Opioid analgesic tolerance is associated with a disruption in Ca^{++} homeostatis. Smith et al. (1999) demonstrated that Ca^{++} influx and mobilization from intracellular pools maintained the expression of morphine tolerance.

From the above review, it appears that, there are diverse effects of the analgesic drugs which need further confirmation and hence, the present study was designed to access the effect of short term and long
term use of different analgesics on various biochemical alterations in the blood leading to their secondary effects on different vital organs of the body especially liver, kidney and heart.