PRODUCT MONOGRAPH

[Pr]CLONIDINE

(Clonidine Hydrochloride)

0.1 and 0.2 mg Tablets

USP

Antihypertensive

Sanis Health Inc.
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THERAPEUTIC CLASSIFICATION

Antihypertensive Agent

ACTION AND CLINICAL PHARMACOLOGY

Clinically, the principal effects seen with CLONIDINE (clonidine hydrochloride) are consistent with a direct action of the drug on the vasomotor centres in the brain stem. There is no blockade of peripheral ganglia, neurons or receptors. In animals, following clonidine administration, spontaneous sympathetic discharges from the medullary centres are reduced. A lowered tone of the vasomotor centres rather than blockade is suggested by the differential action on spontaneous and evoked central sympathetic impulses. Thus, clonidine has the ability to lower blood pressure while preserving normal homeostatic mechanisms.

A pressor phase is not seen if the drug is given intramuscularly or orally, although with intravenous use of the drug a transient rise in blood pressure may precede the prolonged period of hypotension. The pressor phase following intravenous clonidine has been shown to be due to a direct effect of the drug on peripheral α-receptors, and this phase of the blood pressure effect and the depressor phase can be reversed by α-blocking drugs. It has been suggested therefore, that clonidine exerts an action on postulated central α-receptors in a manner similar to the action in the periphery. The prolonged hypotensive phase may thus result from two opposing actions each mediated by α-receptors.

Effects on Catecholamines, Renin and Aldosterone:

Tissue stores of catecholamines are not depleted by clonidine. However, as would be expected with central depression of sympathomimetic activity, clonidine therapy results in diminished urinary excretion of catecholamines. Conversely, there may be a sharp increase in catecholamine excretion over a period of several days on withdrawal of the drug, this presumably representing a rebound effect following release from the drug's action.

Clonidine generally induces a decrease in the production of renin and aldosterone, and these effects follow reduced catecholamine secretion and lowering of blood pressure. The effect of clonidine on catecholamines and blood pressure persists if sodium intake is restricted, yet the stimulus to renin and aldosterone secretion provided by sodium depletion, is not blocked by the

drug. The control of blood pressure shown in this way to be independent of renin and aldosterone levels is further evidence that the hypotensive effect of clonidine is linked to the action on sympathetic function.

In animals, prolonged treatment with clonidine causes a decrease in the responsiveness of the vascular smooth muscle to catecholamines and to angiotensin. This change in vascular response may be of importance in explaining the chronic hypotensive effect in man.

Hemodynamic Effects in Man:

There is virtually no postural change in blood pressure during clonidine administration in most patients. The underlying hemodynamic factors however do differ according to position. Acute administration of clonidine in the supine position, results in a hypotensive effect which is related to a reduction in cardiac output, vascular resistance remaining unchanged. Clonidine thus prevents the rise in peripheral resistance which usually follows a drug-induced blood pressure reduction. In the erect position acute administration of the drug results in a hypotensive effect associated with lowered peripheral vascular resistance and a lesser effect on cardiac output. The reduction in cardiac output which occurs in the supine position results from lowered stroke volume as well as reduced heart rate. Relative preservation of cardiac output in the erect position, on the other hand, appears to be related to the maintenance of stroke volume.

Further circulatory adjustments occur with continued administration of clonidine and the hypotensive effect seen during prolonged therapy is largely due to reduced peripheral resistance.

Renal Hemodynamics and Sodium Balance:

The blood pressure reduction due to clonidine in man, does not cause significant alterations in renal blood flow in the supine position. A consistent decrease in renal vascular resistance is seen in the erect position.

Acute administration of the drug in animals causes a dose related increase in renal vascular resistance without any change in glomerular filtration rate. There is correlation between these effects and increased tubular reabsorption of sodium.

Clinically, there may be some sodium retention and slight weight gain during the initial three to four days of therapy. The sodium is re-excreted thereafter and weight goes down during continued administration of the drug. These transient changes in sodium balance are rarely of clinical significance and are not seen at all if clonidine is given concomitantly with a diuretic.

Effects of Glucose Metabolism:

Although single large doses of clonidine impair glucose handling, presumably because of the transient adrenergic effects described above, no effects on glucose metabolism are seen during the long term use of the drug.

A comparative bioavailability study was performed on CLONIDINE 0.2 mg tablets and Catapres® 0.2 mg tablets. Nineteen healthy male volunteers completed the two-way crossover study. Blood samples were taken at 0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours to determine the mean plasma levels of clonidine. The results of the study can be summarized as follows:

Pharmacokinetic indices for clonidine:

	Geometric Mean Arithmetic Mean (C.V.)				
	CLONIDINE (2 x 0.2mg)		**CATAPRES® (2 x 0.2mg)**		**Percentage of CATAPRES®**
AUC_T (ng•h/mL)	17.46 17.81	(20.05)	17.64 18.19	(25.55)	99
AUC_I (ng•h/mL)	18.92 19.36	(19.80)	19.49 19.93	(24.36)	97
C_{max} (ng/mL)	1.20 1.21	(13.75)	1.17 1.19	(18.29)	102
T_{max}* (h)	2.50	(0.97)	2.89	(1.49)	-
$T_{½}$* (h)	10.31	(3.09)	11.76	(3.67)	-

*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

INDICATIONS AND CLINICAL USE

CLONIDINE (clonidine hydrochloride) has been used successfully to treat hypertension of all grades of severity. It has the ability to lower blood pressure without impairing normal homeostatic mechanisms. The supine and erect blood pressures are nearly identical, and thus in most patients, orthostatic symptoms are very rare. Post exercise hypotension does not occur, and the Valsalva reflex is not blocked by the drug.

Clonidine Used Alone:

Many hypertensive patients can be controlled with the use of clonidine alone and such therapy would have distinct advantages in the long term management of hypertension. There are no changes in serum electrolytes, uric acid or increases in plasma renin due to clonidine. No effects

on glucose metabolism are seen during long term use of the drug. A positive direct Coombs reaction is not produced by clonidine, nor does it lead to the production of anti nuclear factor. Hemolytic anemia has not been reported, and there is no evidence of hepatotoxicity. During prolonged usage renal blood flow is preserved and no deterioration in renal function occurs which is attributable to therapy.

Clonidine used alone has advantages especially for the young mild hypertensive, because this, type of patient faces life long therapy and it is particularly desirable to avoid long term biochemical disturbances.

Clonidine therapy may be initiated with 0.05 to 0.1 mg four times daily, and the dosage may be increased every few days according to response and tolerance. The final dosage, when used alone, ranges between 0.2 and 1.2 mg daily though some severe hypertensive patients have been treated with as much as 5 mg daily. To ensure blood pressure control during sleep, the last dose of the day should be given immediately before retiring. A larger than usual single dose may be conveniently given at this time as the sedative effect of the drug is not, under these circumstances, a limiting factor.

Sedation and dryness of the mouth are the principal side effects which limit dosage. After the first few weeks of therapy these unwanted effects become less evident and thereafter further increases in dosage may be made if it is necessary to reduce blood pressure further. In combatting dryness of the mouth, sucking sour candies may prove helpful.

It may be necessary to adjust the dosage upwards during the first three months of therapy to maintain the response, but thereafter increased dosage is seldom necessary. There have been rare instances of apparent late tolerance which have been attributed to severe emotional upsets precipitated by home circumstances. Admission of such patients to hospital has resulted in restored responsiveness to the same dose of the drug.

Clonidine Used with a Diuretic:

Clonidine has been used successfully together with furosemide and the thiazide diuretics and with chiorthalidone.

A greater fall in blood pressure is produced by the combination of clonidine with a diuretic than either drug alone and this occurs regardless of which drug is administered first. While the effects of the two drugs are additive in the erect position, there appears to be a synergistic effect in the supine position, so that the postural changes in blood pressure are even less than when giving clonidine alone.

To achieve the same degree of blood pressure control when a diuretic is included in the regimen, lower doses of clonidine may be used. In these circumstances, most mild to moderate hypertensives can be controlled using only 0.3 to 0.6 mg of clonidine daily in divided doses.

Severe hypertensives have been successfully treated with a diuretic and higher doses of clonidine (frequently up to 1.2 mg daily and occasionally up to 5 mg daily).

Dosage adjustments should be made over a period of several months when extremely high doses of clonidine are necessary. In this way, sedative effects initially present with each increment in dosage, tend to wear off while the antihypertensive effect persists. Clonidine therapy does not result in the disabling postural symptoms which often limit treatment when using peripheral adrenergic blocking agents.

Clonidine Used With Other Antihypertensive Agents:

The experience with methyldopa added to clonidine therapy indicates that lower dosages than usual of each drug may be employed, thus minimizing side effects, while providing antihypertensive effects.

Further reductions in blood pressure have been achieved when clonidine has been used together with guanethidine, bethanidine and hydralazine.

Pheochromocytoma:

Clonidine is not indicated in pheochromocytoma. However, in contrast to guanethidine and reserpine the drug has no crisis-inducing properties, in this condition.

No false positive or false negative results will occur during the administration of clonidine as the drug does not affect the urinary VMA and catecholamine excretion significantly in patients with. pheochromocytoma.

CONTRAINDICATIONS

CLONIDINE (clonidine hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

If CLONIDINE (clonidine hydrochloride) therapy is discontinued for any reason, withdrawal should be done gradually over several days rather than abruptly. Following sudden discontinuation of high doses of the drug, there have been rare instances of rebound hypertensive crisis. During such episodes, high serum levels of catecholamines have been found. Reinstitution of clonidine therapy at the previous dosage level effectively controls such hypertensive episodes and the drug can subsequently be withdrawn gradually.

If rebound hypertension due to clonidine withdrawal occurs in the context of emergency surgery, control may be achieved by means of intravenous infusions of alpha adrenergic blocking agents.

Intravenous phentolamine in 5 to 10 mg doses at 5 minute intervals up to a total of 30 mg has been used successfully.

Oral clonidine therapy should be recommenced as soon as possible.

If a patient receiving clonidine therapy orally undergoes elective surgery it is important to continue with therapy parenterally throughout the period that oral medication cannot be taken.

PRECAUTIONS

Patients with a known history of depression should be carefully supervised while under treatment with CLONIDINE (clonidine hydrochloride), as there have been occasional reports of further depressive episodes occurring in such patients.

As an abrupt withdrawal of clonidine is followed in some cases by an excess of circulating catecholamines, caution should be exercised in the concomitant use of drugs which affect the metabolism or the tissue uptake of these amines (MAO inhibitors, beta-blockers and tricyclic antidepressants, respectively).

In order to minimize the sedative effect of the drug, the dosage of clonidine should be increased gradually. This is of particular importance in those patients who operate automobiles and potentially dangerous machinery.

A few instances of a condition resembling Raynauds phenomenon have been reported. If patients with Raynauds disease or thromboangiitis obliterans are to be treated with c caution should be observed.

A mucous membrane drying effect on the eyes is produced by clonidine. On rare occasions this had led to corneal ulceration.

Smaller doses of the drug are often effective in treating patients with a degree of renal failure as with any drug excreted primarily in the urine.

The use of clonidine during the first trimester of pregnancy is subject to the normal precautions surrounding the use of any drug at this time. Animal tests have shown no evidence of fetal abnormality, though there was some decreased fertility.

ADVERSE REACTIONS

Initial mild sedation and dry mouth are encountered in a proportion of patients. These effects are seldom severe and usually subside in two to three weeks as treatment continues.

Fluid retention and weight gain may be reported during the initial stages of treatment with CLONIDINE (clonidine hydrochloride). This side effect is usually transient, but the addition of a diuretic will correct any tendency to fluid retention in these cases.

Other occasional drug-related side effects which have been noted in the literature include dizziness, headache, dryness, itching or burning of the eyes, rarely corneal ulceration, nocturnal unrest, nausea, euphoria, constipation, impotence (rarely), and agitation on withdrawal of therapy. At high dosage levels, facial pallor has occasionally been noted.

On investigating blood status, renal function or liver function, no toxic reactions have been observed. A single case of toxic hepatitis in a patient under treatment with clonidine has occurred though the role of the drug remains questionable. Long-term treatment has shown no adverse effect on blood urea nitrogen levels, and on patients with pre-existing renal damage, there has been no further impairment of renal blood flow despite a fall in arterial blood pressure.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The most common signs and symptoms to be expected from overdosage with CLONIDINE (clonidine hydrochloride) include skin pallor, bradycardia, pronounced hypertension, dryness of mouth, and deep sedation or coma. Complete recovery within 24 hours has been produced by gastric lavage and the administration of an analeptic and a vasopressor.

DOSAGE AND ADMINISTRATION

Initially 0.2 to 0.4 mg daily in divided dosage. Increases may be made every few days according to response and tolerance. To ensure blood pressure control during sleep, it is recommended that the last dose of the day be given immediately before retiring to ensure blood pressure control during sleep. Final dosage of CLONIDINE (clonidine hydrochloride) is usually between 0.2 and 1.2 mg daily in divided doses.

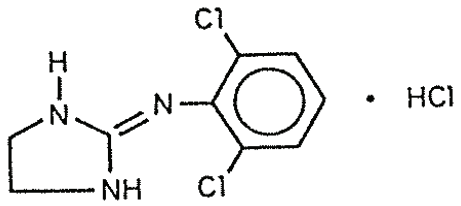
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Clonidine Hydrochloride Tablets

Chemical Name: 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride

Structural Formula:



Molecular Formula: $C_9H_9CI_2N_3$•HCI

Molecular Weight: 266.56

Description: Clonidine hydrochloride is a white, odorless, bitter, crystalline powder. It is soluble in water and alcohol, practically insoluble in chloroform and ether. The pH of a 5% aqueous solution lies between 3.5 and 5.5.

STABILITY AND STORAGE RECOMMENDATIONS:

Store between 15 - 25°C and keep container tightly closed. Boxes of unit dose strips should be stored between 15 - 25°C and protected from high humidity.

AVAILABILITY

CLONIDINE (clonidine hydrochloride) is available as:

0.1 mg - white, round, scored tablet engraved with ‘0.1’ on one side and ‘novo’ on the other, containing 0.1 mg clonidine hydrochloride. Supplied in bottles of 100 and 500 tablets.

0.2 mg - orange, round, scored tablet engraved with ‘0.2’ on one side and ‘novo’ on the other, containing 0.2 mg clonidine hydrochloride. Supplied in bottles of 100 tablets.

PHARMACOLOGY

Pharmacokinetics:

In all species examined, clonidine is well absorbed from the intestine. Plasma levels in the dog, can be detected one hour after administration of an oral dose of 0.52 mg/kg, and maximum plasma levels are reached after 4 to 8 hours. Significant plasma level (0.20 µg % of clonidine) can be detected in man one hour after oral administration of a single dose of 390 µg. Since clonidine is approximately 40 - 50% bound, this reflects an actual free plasma level. Peak plasma levels in man and monkey occur after three hours, and decline with a half-life of twenty hours. After 24 hours, elimination decreases, and is completed only after five days.

Tissue levels are distinctly above blood levels. After either oral or i.v. administration they show similar distribution patterns over heart, liver, lung, spleen, testes, brain, adrenal gland, fat and muscle. The highest concentration of clonidine after oral administration is found in the kidneys and the gastrointestinal tract, but only very small amounts can be detected in these organs 48 hours after administration. There is a high concentration of clonidine in the lacrymal and parotid glands (40 times higher than the blood level).

In the rat, an enterohepatic circulation of clonidine has been described. Within the first 24 to 28 hours, up to 24% of an oral dose is excreted in the bile.

In dogs and monkeys, a large proportion (90 to 95%) of the given dose is metabolized, whereas in humans clonidine is less extensively metabolized. After 48 hours, up to 80% of the administered radioactive clonidine is excreted in the urine of dogs, and up to 18% in the feces. 65% of the orally administered drug is excreted in the urine of man and an estimated 22% in the feces. At 24 hours and 48 hours respectively, 58% and 44% of the activity in human urine is unchanged clonidine.

In man four different metabolites have been detected.

Cardiovascular Effects:

Two opposing actions on the cardiovascular system are observed with clonidine. As an α-sympathomimetic it constricts blood vessels but, it does not directly influence the heart as it seems devoid of β-stimulant action. Tendency to reduce the peripheral resistance and to decrease cardiac output is the result of the very potent inhibitory action on central spontaneous sympathetic activity. In addition, a vagal component appears to be involved, since phentolamine or reserpine abolish the effect on blood pressure but only decrease the bradycardia produced by clonidine, while atropine decreases the hypotension and bradycardia.

Clonidine has neither a ganglionic nor a postganglionic blocking action; it is free of α - and β-adrenergic blocking, actions; it does not act on vagal receptors, and it does not interfere with the catecholamine content of the various tissues.

A biphasic cardiovascular effect of intravenous doses (1 to 100 μg/kg) of clonidine given to animals of different species, either intact or in various experimental preparations is exerted: (a) an initial very brief rise of the blood pressure is followed by; (b) a sustained fall.

(a) The brief vasopressor effect shows the following characteristics: (1) it is not prevented by pretreatment with reserpine; (2) it is abolished by pretreatment with phentolamine; (3) it is reduced by cocaine; (4) it is still elicited in the spinal, decerebrated, decapitated, pithed, immunosympathectomized, bivagotomized, stellate ganglionectomized and debuffered animal; and (5) it is accompanied by bradycardia.

Clonidine, in addition, causes direct vasoconstriction in isolated organs. Clonidine appears to compete with adrenaline and causes an adrenaline-like effect in experiments with isolated smooth muscles of rabbits (non-pregnant uterus, small intestine and blood vessels of the ear).

Contrary to the initial vasopressor effect of guanethidine and bretylium, clonidine does not interfere with the synthesis, storage, or release of catecholamines from the nerve endings, but acts by direct α-adrenergic stimulation. Clonidine is less depressant than guanethidine upon reflex blood pressure responses, as shown by the conservation of the normal diving reflex in ducks and by the absence of effect on the blood pressure response to vertical tilting in dogs. However, clonidine markedly enhances the pressure-induced reflex bradycardia in dogs (total heart-lung bypass); this effect is abolished by stellate ganglionectomy and bivagotomy.

In experimental animals, bradycardia is seen with 5 μg/kg i.v., but total denervation of the heart abolishes any bradycardic response to doses as high as 1 mg/kg. In very high doses it has been shown, however, that clonidine is depressant directly upon the myocardium.

(b) The long lasting, slow-recovering depressor phase of clonidine is clearly dose-dependent and shows the following characteristics: (1) it is inhibited by pretreatment with reserpine or phentolamine; (2) it is absent in the spinal, pithed or decapitated animal; (3) it is elicited by injection of minute quantities (even 1/100 of the intravenous dose) administered directly into the central nervous (intracisternal, intrahypothalamic or intraventricular injection, or infusion into the vertebral arteries); and (4) it is also accompanied by bradycardia, which persists throughout the entire blood pressure response to clonidine.

In dogs and rabbits clonidine reduces the cardiac output. Apparently, this is not due to a direct negative inotropic effect upon the cardiac muscle or to a local action on the pacemaker region, nor does it arise as a reflex response to a change in blood pressure. It is apparently due to a reduction in the sympathetic drive to the heart or to the sympathetic venodilatation caused by the drug. After vagotomy, no change is seen in this cardiac response.

Clonidine decreases the neuronal traffic in the sympathetic nervous system or at least changes the pattern of sympathetic discharges, inhibiting centrally the bulbar sympathetic cardio-accelerator and vasoconstrictor mechanisms. The impulse traffic in the renal, phrenic, cervical, splanchnic, and cardiac sympathetic nerves (pre- or post-ganglionic) in different animal species rapidly decreases after clonidine, and finally disappears. Clonidine does not reduce the discharge in all the sympathetic nerves to the same extent, the cardiac nerve being less affected. This effect is dose-dependent, lasts as long as the hypotension and the bradycardia, and is not influenced by vagotomy nor suppression of afferent input from the peripheral chemo- and baroreceptors. The depression of the sympathetic activity is more effective on the spontaneous discharges than on reflexly or centrally evoked discharges, especially if submaximal or supramaximal stimulation at low frequencies is used. An adrenergic block is not the reason for the decrease in the sympathetic tone since low doses of clonidine potentiate and prolong the blood pressure effect of adrenaline and prolong the responses to noradrenaline.

The biphasic change in arterial blood pressure is accompanied by a corresponding sharp increase and then a fall in total peripheral resistance. In unanesthetized rabbits, the significant reduction in the total peripheral resistance obtained by single intravenous injections of clonidine is unaffected even when the effects of the autonomic nervous system are blocked by pretreatment with phenoxybenzamine, propranolol and atropine. This indicates that clonidine may have a direct peripheral vasodilation action in addition to its effect on the CNS and its peripheral sympathomimetic effect, especially when the level of resting sympathetic activity is low. There is a decreased skin and skeletal muscle blood flow in dogs during the transient pressor phase, but the coronary blood flow is increased, indicating either a lesser degree of vasoconstriction relative to that in other vascular fields, or vasodilatation.

The depressor phase usually shows an increase in the circulatory capacity. There is a corresponding change in the regional distribution of blood in the peripheral circulation; the vascular resistance in the cutaneous and skeletal beds decreases, whereas the cerebral, pulmonary, renal and splanchnic vascular fields show variable responses. A fall in the calculated coronary vascular resistance has been demonstrated in the dog heart-lung bypass preparation with separate coronary and systemic perfused circulation, even when the heart rate was maintained constant.

In cats, chronic oral administration of clonidine at relatively low doses (10 mcg/kg/day for 4 weeks) produced a significant decrease in the responsiveness of the blood vessels to either vasoconstrictor or vasodilator drugs. This effect may contribute to the hypotensive action of chronically administered clonidine.

Effects on the Kidney:

In acute studies, clonidine given intravenously or by infusion into the renal artery diminishes the renal blood flow and reduces the excretion of sodium in dogs. The intravenous or intraperitoneal administration of clonidine to rats however, enhances the diuresis and produces a dose-dependent increase in the excretion of inorganic ions, their relative composition being quite uniform.

Effects on the Central Nervous System:

A dose-dependent sedative action has been demonstrated in acute experiments in cats and dogs receiving i.v. clonidine. There is a reduction of exploratory behaviour in rats and inhibition of pain-induced aggression in doses smaller than or equal to those effective in producing hypotension. Mice and rats have shown exopthalmos, horripilation and intense tremors at 1 to 5 mg/kg, a marked aggressivity at 10 mg/kg, followed by sedation and reduction of spontaneous mobility. The conditioned avoidance behaviour of guinea pigs and rats is inhibited by clonidine, and the young chicken suffers a loss of the righting reflex. Sleep is induced in the young chicken by very small doses (0.02 mg/kg). The depth and the duration of sleep (either behavioural or barbital-or chloral-induced) are potentiated by clonidine in rat, mouse and cat. Clonidine, given i.v., produces in rabbits a typical resting EEG. The rat EEG shows synchronization, slower waves and a decrease of faster waves.

The drug has an analgesic action in mice, as these animals do not take up their usual defence and escape reaction. At very high doses a local anesthetic action has been observed. Clonidine closely resembles the typical local anesthetic procaine, as shown by electrophysiological studies of intracellular action potentials and membrane resistance and firing threshold of the crayfish stretch receptor. The local anesthetic effect of clonidine appears to be much more potent than the effect produced by tetracaine on the rabbit cornea.

Effect on Salivation and Gastric Secretion:

The conditioned salivation in dogs is greatly reduced by clonidine, but has no effect upon the salivation produced either by pilocarpine or by stimulation of the chorda tympani. The most likely action of the drug is upon central nervous centres controlling salivation, and not by a peripheral effect. Clonidine, given intravenously, inhibits the gastric secretion and reduces its acidity in rats, thus giving protection against stress- and reserpine-induced ulcers and gastric hemorrhage, but it is ineffective against histamine- and serotonin-provoked ulcers.

Metabolic Effects:

Intravenous administration of clonidine to the rat increases the pool, life and turnover of body glucose and decreases glucose oxidation. There is no change in muscle glycogen, but liver glycogen is lowered. In cats receiving clonidine, a dose dependent hyperglycemia has been

described (infusion of 10 μg/kg in the vertebral arteries provokes a 30% higher level than control), but this effect is less marked in adrenalectomized animals.

With very high doses only rabbits show hyperglycemia. Normal and fasting rats also show increased plasma glucose levels after clonidine given by different routes.

Clonidine does not affect the plasma level of free fatty acids, but with very high doses has increased the plasma renin level in rats.

TOXICOLOGY

The acute toxicity values identify clonidine as a substance with an unusually wide therapeutic margin. When given intravenously to mice, the LD_{50} in 24 hours is 17.5 mg/kg; during a 14-day observation period following a single oral dose, the LD_{50} is over 30 mg/kg in dogs.

Subacute and Chronic Toxicity:

Subacute toxicity studies of 12 to 13 weeks and chronic toxicity studies of 26 to 78 weeks have ruled out any increased morbidity or mortality due to a cumulative effect or possible organ damage. No significant drug induced pathological or histological change in the circulatory and parenchymatous organs of the rat or in the endocrine organs of mice and rabbits have been observed. After subacute dosages, no abnormality has been recorded in blood, urine or internal organs. There is a clear dose-related lag in weight gain, and sedation with a brief hyperactive phase immediately following the administration of the drug in rats. Dogs show a dose- related restriction of growth; female dogs in subacute i.v. toxicity studies were anovulatory with high daily doses (0.5 mg/kg). In rabbits receiving 1 mg/kg daily for 30 days, glycosuria has been found.

Rats are nocturnal animals and they show spontaneous retinal atrophy with aging. The atrophy is directly related to the intensity of light, and is completely avoided by excluding light. The apparent intensification of this phenomenon in rats receiving clonidine is related to the dose-dependent mydriasis produced by the drug. Clonidine treated rats with one eye sutured to exclude light show retinal atrophy only in the contralateral eye. Hypertensive patients treated with clonidine for periods of time varying from one month to over 24 months failed to show any ocular changes related to the drug after ophthalmological examination.

Tolerance to clonidine has not been demonstrated in either dogs or in rats, as shown by two exactly measurable parameters (mydriasis and bradycardia).

Reproduction Studies:

Teratogenicity and embryotoxicity studies have been carried out in rats, mice and rabbits. No deaths or manifestation of intolerance have been observed among the mothers, but a decreased fertility and a decreased number of offspring both manifest embryotoxicity with high doses.

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