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Original Article

STUDY OF ONSET AND DURATION OF SEDATIVE EFFECT OF CLONIDINE WITH VARIOUS ROUTES OF ADMINISTRATION IN WISTAR ALBINO RATS

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ABSTRACT
The aim of present study is to demonstrate the sedative effect of Clonidine, along with its onset &duration of action with oral, intraperitoneal & intravenous routes of administration in Wistar Albino rats. Two well established methods were adopted these include actophotometer and rota rod. In the present study rapid onset of sedation is observed with intravenous administration of Clonidine where as longer duration of sedative effect is observed with intraperitoneal administration.

Keywords: *Clonidine, Wistar albino rats, Actophotometer, Rota rod*

INTRODUCTION

Clonidine is a selective partial agonist for α_2-adrenergic receptors. α_2- agonists have both peripheral and central effects on the cardio-vascular system. Acting centrally, Clonidine causes hypotension and bradycardia. Clonidine inhibits the release of adrenaline from prejunctional nerve endings. It also produces marked sedation and anxiolysis, decreases spontaneous motor activity and potentiates the sedative and anesthetic actions of other drugs [1].The central α-adrenoceptors responsible for mediating Clonidine-induced sedation in rats have been characterized according to their sensitivity to α-adrenoceptor agonists and antagonists. The relative potencies of the agonists in causing sedation and of the antagonists in inhibiting the sedative effect of Clonidine clearly demonstrated that the central α-adrenoceptors mediating Clonidine induced-sedation is the same as the peripheral presynaptic α_2-adrenoceptors.Clonidine is a mixed α_1 and α_2-adrenoceptor agonist with a predominant α_2-action. Traditionally, it has been used as an antihypertensive agent since the late sixties. The major hemodynamic effects results from stimulation of α_{2a}- present mainly post junctionally in medulla [2]. One of the most common side effects of the treatment of hypertension with Clonidine is sedation which, like the hypotensive action, results from the stimulation of central α-adrenoceptors. However the central α-adrenoceptors mediating the sedative effect of Clonidine are not identical with those in peripheral vascular smooth muscle [3,4]. It is now well established that peripheral α-adrenoceptors fall into two different groups and are classified as α_1 and α_2. The α_2-adrenoceptors have been identified on the terminals of sympathetic nerves supplying the rabbit and rat heart [3, 5] and rabbit pulmonary artery, the motor nerves to the rat vas deferens and the cholinergic nerves of the guinea-pig myenteric plexus.

MATERIAL AND METHODS

Albino rats (150-200gms), Clonidine (25mcg), Acto-photometer **(Fig - 1)**: This operates on photocells which are connected in circuit with a counter. When the beam of light falling on the photocell is cut off by the animal, a count is recorded. An actophotometer could have either circular or square area in which the animal moves. Both rats and mice may used for testing in this equipment [7].

Rota rod **(Fig - 2)**: The rota rod was based on that described by Jones & Roberts (1968) [2]. It was 3.2 cm in diameter and accelerated linearly from 0 rev/min at time 0 to a maximum of 50 rev/min at 5 min (Figure 2).Eustachean catheter (18-20guage), Syringes & needles.

The animals were acquired from the animal house of Dr VRK Womens medical college. The animals were maintained under standard laboratory and standard diet. The animals were put on overnight fasting and acquired for the study. Animals were divided into three groups for the three different routes of administration i.e. oral, intra-peritoneal and intravenous. Each group consisted of 10 rats. The drug solution was prepared in distilled water to contain 25 mcg/ml. First group was given 25 mcg of Clonidine through oral route, second group through intraperitoneal route and the third group through intravenous route. The onset and duration of sedation was observed using actophotometer, which records the motor activity of animals by counting number of movements before and after the administration of drug. The first parameter motor activity taken as normal when there are 200 movements for 5 minutes. The onset of sedation was considered when there was a50% reduction in this count and has been recovered when they attain pretreatment values. The second parameter was noting the muscle relaxation on Rota road. The time of fall from the rotating rod was noted before and after the administration of drug. The normal reading on Rota rod was considered on rotating rod for atleast 180 sec and the onset sedation was considered when they are unable to retain on rod for atleast 90 sec and recovered when they attain the pretreatment readings. Above both readings were taken immediately and after every ten

min of drug administration for first hour and test was repeated every thirty minutes until they regained their pretreatment readings. The Rota rod was compartmented so that 6 rats could be tested simultaneously. The rats were removed from their home cages, injected with drug or vehicle and returned to their cages for the duration of the dose test interval. The rats were then placed on the rod facing the direction of rotation. When the Rota rod was set in motion, a digital timer for each compartment started and stopped automatically when the rat fell from the rod. The locomotor activity was measured using an actophotometer.

Statistical analysis: was done by ANOVA.

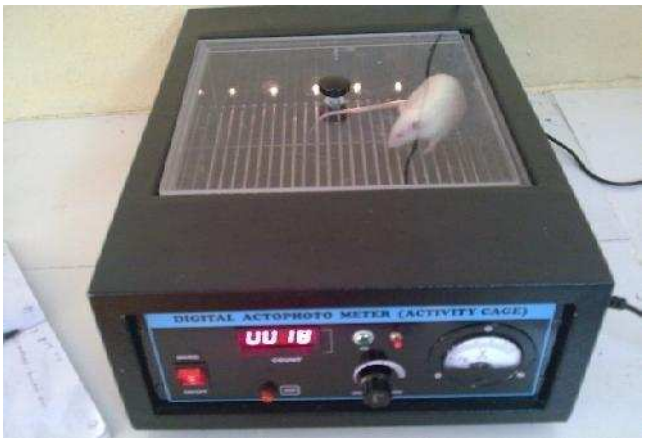

Fig1: Actophotometer

Fig 2: Rota rod

It was observed that when Clonidine was given by oral route the onset of action assessed by motor activity (actophotometer) is 15 min with SD 3.333 and SEM 1.055, by intraperitoneal route it is 10 min SD 1.633 and SEM 0.5164 and by intravenous route it is 1 min SD 0.667 and SEM 0.2108, the p value being 0.000 which is significant (**Table - 3**)(**Fig - 3**).Onset of sedation assessed by muscle relaxation(Rota rod) in oral route is 30 min SD 2.357 SEM 0.8028, in intraperitoneal route it is 15 min with SD 2.539 and SEM 0.7455 and in intravenous route the onset of sedation is 0.25 min SD 0 SEM 0, the p value being 0.000 which is significant(**Table - 4**)(**Fig - 3**).The duration of sedation by motor activity (actophotometer) in oral route it is 5 hrs SD 13.33 SEM 4.216, in intraperitoneal route it is 9.66 hrs SD 13.33 SEM 4.216 and by intravenous route the duration of sedation is 3.96 hrs SD 17.51 SEM 5.538,p value is 0.000 which is significant(**Table - 5**)(**Figure - 5**).The duration of sedation by muscle relaxation (Rota rod) in oral route it is 3.96 hrs SD 14.76 SEM 4.667, in intraperitoneal route it is 8.25 hrs SD 6.667 SEM 2.106 and by intravenous route the duration of sedation is 6 hrs SD 13.33 SEM 4.216, p value being 0.000 which is significant (**Table - 6**)(**Fig - 4**). It was observed that in albino rats with intravenous administration of 25mcg of Clonidine, there was rapid fall (1 min) in the locomotor count than with other routes. The fall in locomotor activity was maintained for a prolonged period (mean duration of 9.40hrs) with 25mcg of Clonidine administered intraperitoneally as compared with other routes. It was observed that in albino rats with intravenous administration of 25mcg of Clonidine, there was rapid decrease (15sec) in muscle grip than with other routes. The fall in muscle grip was maintained for a prolonged period (mean duration of 8.15 hrs) with 25mcg of Clonidine administered intraperitoneally as compared with other routes. Recovery from sedative effect of Clonidine is prolonged with oral route when compared to intravenous route which is 1.30 more than intravenous route when you take motor activity as parameter (**Table - 1**) the recovery period is 10 hrs with intraperitoneal route which is almost to the intravenous route (**Table - 1**).When muscle relaxation is taken as parameter the recovery from sedation with intraperitoneal route double (8.30 hrs) the oral route (4.30 hrs) (**Table - 1**).Recovery from intraperitoneal route is more2.30 hrs (8.30 hrs) when compared to intravenous route which is 6 hrs (**Table - 1**)

RESULTS

Table 1: Clonidine induced onset and duration of sedation by different routes of drug administration observing by motor activity and muscle relaxation

	Oral route			Intraperitoneal route			Intravenous route		
Parameter	**Onset**	**Recovery**	**Duration**	**Onset**	**Recovery**	**Duration**	**Onset**	**Recovery**	**Duration**
Motor activity(200)	15 min	5 hr 30 min	5 hr 15 min	10 min	10 hr	9 hr 40 min	60 sec	4 hrs	3 hrs 59 min

Table 2: **Clonidine induced Sedation observed by Actophotometer and Rota rod**

S.NO	ROUTES	ONSET		DURATION	
		MOTOR ACTIVITY (in min)	MUSCLE RELAXATION (in min)	MOTOR ACTIVITY (in hrs)	MUSCLE RELAXATION (in hrs)
1	ORAL	15	30	5	4
2	INTRA PERITONIAL	10	15	9.40	8.15
3	INTRAVENOUS	1	0.25	4	6

Table 3: Onset of sedation is assessed by Motor activity in different routes of Administration with Clonidine (25mcg)

ROUTES	MEAN (in minutes)	STANDARD DEVATION	STANDARD ERROR MEAN	P-VALUE
ORAL	15	3.333	1.054	0.000
INTRA PERITONEAL	10	1.633	0.5164	
INTRAVENOUS	1	0.6667	0.2108	

Table 4: Onset of sedation is assessed by Muscle relaxation in different routes of Administration with Clonidine (25mcg)

ROUTES	MEAN (in minutes)	STANDARD DEVATION	STANDARD ERROR MEAN	P- VALUE
ORAL	30	2.539	0.8028	0.000
INTRA PERITONEAL	15	2.357	0.7454	
INTRAVENOUS	0.25	0	0	

Table 5: Duration of sedation is assessed by Motor activity in different routes of Administration with Clonidine (25mcg)

ROUTES	MEAN (in hours)	STANDARD DEVATION	STANDARD ERROR MEAN	P- VALUE
ORAL	5.3	0.4216	0.1333	0.000
INTRA PERITONEAL	9.42	0.3458	0.1093	
INTRAVENOUS	6	0.2357	0.07454	

Table 6: Duration of sedation is assessed by Muscle relaxation in different routes of Administration with Clonidine (25mcg)

ROUTES	MEAN (in hours)	STANDARD DEVATION	STANDARD ERROR MEAN	P-VALUE
ORAL	4.2	0.4216	0.1333	0.000
INTRAP ERITONEAL	8.135	0.1107	0.035	
INTRAVENOUS	6	0.3333	0.1054	

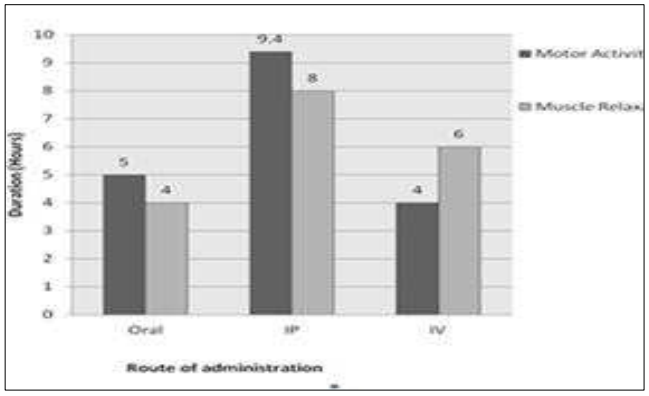

Fig3: Showings mean onset time in three different routes

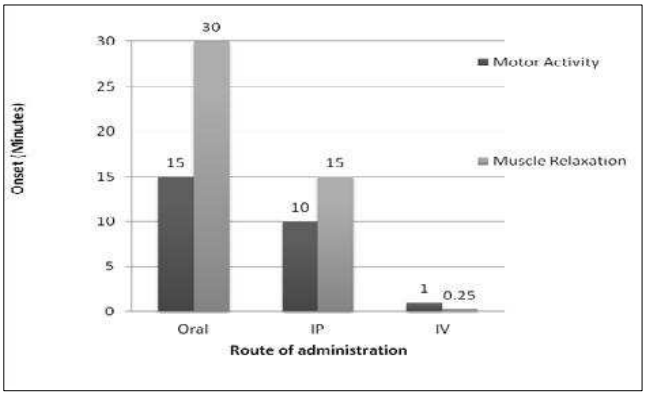

Fig 4: Showings mean duration of sedation

DISCUSSION

The central α-adrenoceptors responsible for mediating Clonidine-induced sedation in rats have been characterized according to their sensitivity to α-adrenoceptor agonists and antagonists. Clonidine injected intraperitoneally, caused dose dependent sedation, both in terms of reduction in the time that rats could remain on an accelerating Rota rod and in terms of overt sedation assessed visually [2].Clonidine an imidazole, $\alpha_2$selective adrenergic agonist was synthesized in early 1960s. During clinical testing of the drug as a topical nasal decongestant Clonidine was found to cause hypotension, sedation and bradycardia. Clonidine as an imidazole binds to imidazoline receptors in addition to $\alpha_2$receptors .Clonidine is mainly used for treatment of hypertension. Clonidine, an $\alpha_2$agonist is a known antihypertensive agent. Because of its sedative and analgesic effects it has gained immense popularity in anesthesiology. Now a days It is used to premedicate children, as an adjuvant to regional and general anaesthesia. And is used it has several other applications in pediatric anaesthesia and is used in the pediatric intensive care as a sedative, analgesic and to ensure hemodynamic stability [5]. The major adverse effects of Clonidine are dry mouth and sedation. The major Therapeutic use of Clonidine is in the treatment of hypertension, in reducing diarrhea in some diabetic patients in autonomic neuropathy and in treating for withdrawal from narcotic, alcohol and tobacco addiction. Preoperatively to decrease the requirement of anesthetic, in anaesthesia for preoperative sedation, anxiolysis, drying of secretions and analgesia. Clonidine produces sedation by decreasing the sympathetic nervous system activity and the level of arousal. The result is a calm patient who can be easily aroused to full consciousness [7].

To study the sedative effect (hypnosis), Phenobarbital is used experimentally in albino mice and rats usually. As Clonidine is used for pre operative sedation and anxiolysis, the present study was conducted to see the sedative effect of Clonidine with three different routes of administration i.e. oral, intraperitoneal and intravenous in albino rats. Most of the central nervous system drugs influence the locomotor activity and muscle tone in human and animals. The parameters considered for the sedative effect of Clonidine were motor activity, which was done through actophotometer and muscle relaxation done through Rotarod.

It is observed that Recovery from sedative effect of Clonidine is prolonged with intraperitoneal administration. It is assumed that is due to slow absorption of the drug Clonidine when given intraperitoneally.

CONCLUSION

The present results confirm earlier reports that Clonidine causes sedation in animals [4]. This effect was seen when Clonidine was administered orally, intraperitoneally and intravenously. According to evaluation using above parameters with three different routes, it is assumed that rapid onset of sedation is observed with intravenous

administration of Clonidine where as longer duration of sedative effect is observed with intraperitoneal administration. These differences in time of onset and duration of sedative effect with different routes can be ascertained to its rate of absorption in different routes and time taken to reach its site of metabolism respectively.

Conflict of Interest: Nil

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