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Scoring Of Central Neurotoxicities of Aminoglycoside Antibiotics - An Experimental Study in Albino Rats

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ABSTRACT

Background: Aminoglycoside antibiotics are still the drug of choice in variable conditions like resistant tuberculosis and septicaemia. Toxic effects are the greatest hurdle in their liberal use. Their central neuro-toxicities specially in terms of affinity are yet to be explored. **Methods:** Experimental rats received streptomycin, kanamycin and gentamycin in a dose of 30mg/kg, 400mg/kg and 135 mg/kg respectively, IMI, daily for 21 days. Total lipids, phospholipids, cholesterol and gangliosides were estimated in auditory cortex, medial geniculate body, inferior colliculus, cerebellum and spinal cord in both control and experimental rats. **Results:** On the basis of statistically significant alterations in aforementioned biochemical parameters, affinity of drugs was quantified by scoring. Streptomycin and kanamycin showed maximum toxicity in terms of scoring of 4 with preferential targets i.e. medial geniculate body and inferior colliculus respectively. Gentamycin showed affinity for higher centres only with equal scoring of 3 for toxicity at three locations i.e. auditory cortex, medial geniculate body and inferior colliculus. **Conclusion:** Such preferential toxicities might reflect some aspects of mechanism of toxicity of different drugs.

Keywords: *Aminoglycosides, Streptomycin, Kanamycin, Gentamycin, Neomycin, Neurotoxicity.*

INTRODUCTION

Streptomycin, Kanamycin and Gentamycin are most commonly used aminoglycoside antibiotics. Their toxicities on central nervous system have already been established[1-4].

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Their preferential effects are also known to exist. The most important side effect of parenteral kanamycin therapy is damage to the auditory portion of acoustic nerve while streptomycin, after prolonged use, produces vestibular disturbances as well as auditory impairment.[5] Gentamycin is also a highly ototoxic drug.[4] Their effects on hearing and balance prompted us to consider auditory cortex, medial geniculate body, inferior colliculus, cerebellum and spinal cord as regions of central nervous system for present study. Lipids are essential components of all cellular structures in the brain.[6] Lipids of various tissues are known to exist in a dynamic steady state with continuous replacement of existing molecule by new ones.[7] We undertook the present study to find out the alteration in the contents of total lipids, phospholipids, cholesterol and gangliosides in aforementioned regions of central nervous system after intoxication of animals with aminoglycoside antibiotics. A statistically significant change in value was considered as indication of degeneration. Till date no report is available quantifying the toxicities produced by said drugs in central nervous system. Present teams of scientists have made an attempt to score the extent of toxicities produced by drugs under consideration in different regions of central nervous system. This will give relative preferential and differential effects of drugs possibly helping in explaining the mechanism of toxicities.

MATERIALS ANDMETHODS

Thirty six white albino Wistar rats weighing 200 ± 10 gm were used for this study. They were fed green vegetables (grass and spinach) ad libitum and had ready access to tap water. They were divided into three groups of twelve animals each. Each group was further divided into control and experimental subgroups of six animals each. Experimental rats of first group received streptomycin sulfate (Ambistryn- S, Sarabhai), 30mg/Kg, IMI., daily for 21 days. Experimental rats of second group received kanamycin sulfate (Kancin, Alembic), IMI, 400mg/kg, daily for 21 days. The third experimental animals were given gentamycin (Pharmaceutical Company of India) in a dose of 135 mg/Kg body weight intramuscularly daily for 21 days. Control rats in all three groups received isotonic normal saline through the same route for the same period. All the rats were stunned and decapitated on day 22. Brain and spinal cord were dissected out on an ice plate. Auditory centre, medial geniculate body, inferior colliculus, cerebellum and spinal cord were separated and were homogenized in a glass homogenizer with a Teflon pestle in chloroform–methanol (2:1) according to the method of Folch et.al. [8]Total lipids, phospholipids, cholesterol and gangliosides were estimated according to the methods of Woodman and Price[9], Marinetti[10], Bloor et. al.[11] and Pollet et. al.[12] respectively.

Data were analyzed statistically using Student's 't' test. Statistically significant increment or decrement of biochemical parameters were considered to be degenerations of nervous regions.

To find out the extent of degeneration, scoring was done. One point was allotted for every statistically established damage. The symbol of '+' was selected for the damage if it was due to increment of parameter and '-' if it was due to decrement of biochemical parameters.

RESULTS

[Table 1] was showing significant increase in total lipids in medial geniculate body, cerebellum and spinal cord caused by streptomycin. Kanamycin affected the level of total lipids only in inferior colliculus. Total lipids were increased in the regions i.e. auditory cortex, medial geniculate body and inferior colliculus by gentamycin.

Levels of phospholipids were well documented in [Table 2]. Streptomycin has resulted into an increase of phospholipids is medial geniculate body inferior colliculus and cerebellum. Kanamycin caused a decrease in the level of phospholipids in auditory cortex and increase in the same in inferior colliculus. Gentamycin led to increase in the level in auditory cortex and medial geniculate body.

[Table 3] was showing the level of cholesterol increased in medial geniculate body and spinal cord by streptomycin, in auditory cortex and inferior colliculus by kanamycin and in auditory cortex, medial geniculate body and inferior colliculus by gentamycin.

Effects of drugs on ganglioside levels have been shown in [Table 4]. Streptomycin increased this level in medial geniculate body and inferior colliculus while gentamycin caused an increment in inferior colliculus only. Kanamycin led to increase in ganglioside level in inferior colliculus. Both streptomycin and kanamycin resulted into reduction in the said level in cerebellum and spinal cord.

[Table 5] has shown scores obtained by three drugs in terms of toxicities in different regions of central nervous system. Streptomycin was found to be toxic in all the regions except auditory cortex which was immune to drug. It scored maximum of 4+ for medilal geniculate body and minimum of 2+ for inferior colliculus. Kanamycin was found to be maximally toxic on inferior colliculus scoring 4+ and minimal on auditory cortex, cerebellum and spinal cord scoring 1- each. Gentamycin was toxic on auditory cortex, medial geniculate body and inferior colliculus, scoring 3+ each.

Table 1: Total lipids in CNS after aminoglycoside antibiotic intoxication (mg/g).

Regions	Control	Streptomycin	Kanamycin	Gentamycin
Aud. cortex	108.32±18.18	110.83± 12.89	981.50±8.86	160±11.38**
Med. gen. body	162.69±14.35	298.38±38.35 *	145.46±18.38	250.75±10**
Inf. colliculus	118.28±18.55	208.80±59.69	188.78±20.4**	180±28.13**
Cerebellum	136.29±15.50	260.46±30.23**	150.39±20.61	148±18.11
Spinal cord	158.39±18.63	239.68±15.19**	190.46±30.22	170±20.23

P value * < 0.01, ** <0.001

Table 2: Phospholipids in CNS after aminoglycoside antibiotic intoxication (mg/g).

Regions	Control	Streptomycin	Kanamycin	Gentamycin
Aud. cortex	38.31±8.63	40.64±3.2	13.80±3.69**	60.74±3.29**
Med. gen. body	20.24±6.32	69.33±10.02**	22.36±3.29	40.57±4.39**
Inf. colliculus	18.36±4.83	42.69±25.77*	32.06±6.12**	25.36±8.59
Cerebellum	20.39±5.23	60.33±7.01**	28.33±10.11	30.48±4.60
Spinal cord	29.63±6.11	40.18±13.01	32.12±8.67	31.18±5.71

P value * < 0.01, ** < 0.001

Table 3: Cholesterol in CNS after aminoglycoside antibiotic intoxication (mg/g).

Regions	Control	Streptomycin	Kanamycin	Gentamycin
Aud. cortex	18.85±2.83	26.61±3.08	16.26±3.89*	27.84±1.30**
Med. gen. body	16.23±6.29	43.68±4.82**	20.04±6.18	34.1±1.36*
Inf. colliculus	17.66±5.95	32.82±9.66	36.18±6.66**	43.60±2.18**
Cerebellum	20.33±5.11	30.33±12.88	28.35±6.72	27.87±3.19
Spinal cord	21.67±6.33	46.81±8.33**	26.49±8.33	29.33±4.66

P value * < 0.01, ** < 0.001

Table 4: Gangliosides in CNS antibiotic intoxication after aminoglycoside (mg/g).

Regions	Control	Streptomycin	Kanamycin	Gentamycin
Aud. cortex	1.33±0.11	1.44±0.14	0.87±0.14	1.33±0.05
Med. gen. body	0.49±0.16	1.88 ±0.23*	0.55±0.17	0.81±0.40
Inf. colliculus	0.26±0.03	1.83±0.13**	0.66±0.02**	1.05±0.09**
Cerebellum	0.79±0.06	0.26±0.001**	0.49±0.06*	0.67±0.07
Spinal cord	0.46±0.04	0.24±0.002*	0.13±0.04**	0.51±0.03

P value * < 0.01, ** < 0.001

Table 5: Scoring in terms degeneration of different regions of central nervous system by streptomycin, kanamycin and gentamycin; **'+'** , increment ; **'-'** decrement.

Regions	Streptomycin	Kanamycin	Gentamycin
Auditory cortex	Nil	-	+ + +
Medial geniculate body	+ + + +	Nil	+ + +
Inferior colliculus	+ +	+ + + +	+ + +
Cerebellum	+ + -	-	Nil
Spinal cord	+ + -	-	Nil

DISCUSSION

Central neurotoxic effects are known to occur due to administration of streptomycin, kanamycin and gentamycin.[3,13,14] Our results regarding effects of streptomycin and kanamycin on four parameters i.e. total lipids, phospholipids, cholesterol and gangliosides on different regions of central nervous systems confirm with previous reports. [1,13,14] We have estimated all four lipid constituents of gentamycin also to compare the toxicities of three drugs [Table 1-4]. Streptomycin and Kanamycin were found to be maximally toxic (Score, 4+) but showed preferential effects i.e. on medial geniculate and inferior colliculus respectively [Table 5]. Preferential toxicities of aforementioned two drugs are well documented.[14] Gentamycin on the other hand exhibited uniform level of toxicities (Score 3+) on auditory cortex, medial geniculate body and inferior colliculus. Cerebellum and spinal cord were found to be immune to gentamycin, scoring nil [Table 5]. Although

gentamycin did not show differential, effects but streptomycin and kanamycin did show. Streptomycin led to statistically significant increase in ganglioside in medial geniculate body and inferior colliculus but reductions in the same in cerebellum and spinal cord [Table 4]. Kanamycin showed very interesting phenomenon i.e. the region dependent differential effect for different parameters. Biochemical parameters were reduced in auditory cortex, cerebellum and spinal cord while increased in inferior colliculus [Table 5].

Preferential effects of aminoglycoside antibiotics have been reported in connection with their peripheral toxicity, because of which streptomycin mainly shows vestibular disturbances while kanamycin affects predominantly on the cochlea.[15] Further studies with the help of radioactive isotope labelling and estimation of different enzymes associated with lipid metabolism may lead to a better understanding of the streptomycin, kanamycin and gentamycin in toxications.

CONCLUSION

Preferential toxicities might reflect some aspects of mechanism of toxicity of different drugs.

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