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Influence of Yogasanas on the Physiology, Therapy and Theophylline Pharmacokinetics in Bronchial Asthma Patients

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Abstract

Bronchial asthma is one of the commonest diseases of concern to medical and allied professionals, affecting 5-10% of the general population. Various therapeutic approaches being practiced in the management of bronchial asthma aim at symptomatic level rather than curative. Long term pharmacotherapy has been associated with higher risks of increased severity, adverse reactions, frequency of attacks and increased medication requirements. The three-fold limitations of the treatment procedure in vogue demand the promotion of a heritage, yoga practices on war-footed basis. Our studies reassess the asthmatic to lead a very happy, comfortable and productive life. Physiological parameters such as pulse rate, respiratory rate, breath holding time and general health were found to be significant in the training period of 30 days and could be explained on the basis of the improvised neurohumoral and psychological controls. Influence of thirty days of practice of yogasanas on the disposition of pharmacokinetics of theophylline SR (200mg) was taken and biological half-life was found to be less in the yoga group than in the non-yoga group.

Keywords: Bronchial Asthma, Yogasanas, Theophylline, Pharmacokinetics.

Introduction

Bronchial asthma has been growing in prevalence and has imposed an increasingly large burden on the health services since at least the middle of the twentieth century (Clark *et al.*, 2000; Jain *et al.*, 1993). This disorder affects an estimated 5-10% of the population, and as such is a major health care issue in most countries. Until recently, study and treatment had emphasized the mechanism of acute bronchospasm and the control of airway smooth muscle tone (Busse *et al.*, 1998). Despite advances in therapy, asthma continues to be a serious health problem associated with significant morbidity and high costs (Revicki *et al.*, 2006). Bronchial asthma is characterized by increased responsiveness of bronchi to various stimuli, manifested by widespread narrowing of the airways that reverses either spontaneously or as a result of treatment. Approximately 30% of infants will wheeze during the first year of life.

Two thirds of these will have reduced airway caliber and the other one third are usually atopic and will continue to wheeze and manifest as childhood asthma. (Landam, 1996). Asthma is one

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of the leading causes of school absences and hospitalization for children, (Clark *et al.,* 1999) which can be interfered with both their academic and social development, (Taylor *et al.,* 1992) although the onset of asthma cannot be prevented and cannot be cured (Wang *et al.,* 2006).The various therapeutic approaches available and being practiced in the treatment of asthma aim at symptomatic level than curative (Kumar *et al.,* 1997). The treatment by most of the systems of medicine involves the life long medication, and chronic medication leads to increased cost of treatment & side effects (Nagendra *et al.,* 1986).

Yoga, is not a system of medicine, is a holistic science with the principles and practices, which can be effective to deal with some of the health problems. Unity in diversity forms the core of Indian culture that offers a grand note of cohesiveness among various practices with this catholicity in understanding. When persons follow one or more of these paths, they allow a harmonious and total growth of the personality (Nagendra *et al.,* 1996). Yogasanas like pranayarna has proved fact based on various yogic practices relieve chronic respiratory ailments like bronchial asthma and chronic bronchitis (Makwana *et al.,* 1988). The voluntary control of breathing may be useful adjuvant in the treatment of patients with chronic obstructive lung disease and bronchial asthma (Singh *et al.,* 1990).

Theophylline a methyl xanthine has been a corner stone of asthma therapy through the years. Theophylline appears to exert its primary influence through inhibition of the type III or IV phosphodiesterase (PDE) which breaks down cyclic AMP in smooth muscle cells, there by leading to an increase in intracellular cyclic AMP concentration (Mulson, 1995).

Materials and Methods

Theophylline tablets (SR 200mg) marketed product from Okasa pharma Ltd.

Theophylline, pure sample was obtained from Cipla Private limited, Bangalore. Caffeine pure sample was procured form Ranbaxy laboratories, Punjab. Chloroform and Isopropanol were obtained from Sisco laboratories, Mumbai. HPLC grade methano'l was purchased from E. Merck, India. Water for HPLC was purchased from Qualigens fine chemicals, Mumbai.

HPLC (Shimpack), Column: C-18, Mobile phase: Methanol: Water (30:70), Flow rate: 1.0 ml/minute, λ_{Max}: 280nm.

Retrospective review of the hospitalized bronchial asthma patients for the management of severe attacks, a 350 bedded hospital in Mysore city was approached and patient profiles were consolidated for the management of severe attacks. To reassess the influence of yogasana exercises on the physiology and therapeutic benefits for bronchial asthma patients, 1 hr yogasana training program was organized for 30 days daily between 7.00 am-8.00 am. Patients were periodically monitored for their PEFR (using peak flow meter), pulse rate, breath holding time, chest expansion, frequency and severity of attacks and medication requirements. The medication information of asthma patients practicing yogasanas were collected before and during the yogasana practice and this study aims to bring the influence of yogasanas on the pharmacokinetics of theophylline.

Eleven patients were examined for hematological and urine profiles and were grouped in to yoga group consisting six patients and non-yoga group consisting five patients. Yoga group patients practiced yogasanas for 1 hr daily for one month and they were abstained from consuming coffee, tea and other beverages and smoking.

The patients were fasted overnight and next day received an oral administration of one 200 mg

theophylline SR tablet with 3 slices of bread and 200 ml of milk. Saliva sampling was done after 0, 1,2,3,4,6,8,10,12 and 24 hrs of dosing. 200 ml of lime juice was given to each patient 3 hours after drug administration. A standard lunch was provided 5 hrs after drug administration, 200ml of mango juice was given to patients 11 hrs post dosing. Throughout the study patients were kept ambulatory and strenuous exercise was avoided. Saliva samples were stored at -24°C until analysis.

One ml of saliva was taken for the analysis from each sample and was mixed with 20 ml of internal standard and shaken for 1 minute. The saliva samples were then extracted with a 10 ml mixture of Chloroform: Isopropanol (95:5) for 30 minutes by simple vortexing. The samples were then centrifuged for 5 minutes at 1500 rpm. The organic layer was separated and evaporated to dryness. The samples were then reconstituted in 1 ml of methanol and 20 µl of reconstituted samples were injected in to the column.

A standard plot was prepared by spiking fresh saliva sample with known amount of pure theophylline and the internal standard (caffeine). A standard graph of peak-area ratio v/s concentration plot was used for reading the concentration of the samples. Pharmacokinetic parameters were determined by using semi log plot of saliva concentration v/s time. C max and T max were directly read from the graph. The slope of the terminal part of the graph was used to calculate elimination rate constant and biological half- life ($t_{1/2}$). The area under the curve (AVC) from 0-24 hrs was calculated by trapezoidal rule.

Results

Table 1a depicts that from year by year number of patients suffering from bronchial asthma is increasing, and % mortality has also increased. It is evident from Table 1b that the factors like hereditary, perennial, seasonal, and allergy definitely influence the number of attacks, which indirectly affect the cost, and time of treatment. To this extent, the observation of applying other system of medicine was also considered. Table 2a and Table 2b are almost self explanatory showing that yoga exercises greatly influence the bronchial asthma attacks to a positive side from which can be assessed that yoga plays a vital role in the treatment of bronchial asthma. Table 3 evidently shows that during the practice of yogasanas, no medication is required and Table 4 shows the pharmacokinetic patterns of theophylline in both the yoga and non-yoga groups.

Table No.1a. Hospitalized Patient- Profiles

Year	Total No. of Patients	Male	Female	Male Child	Female Child	Discharged	Expired	%Mortality
1993	250	120	124	5	1	245	5	2
1994	189	88	94	4	3	186	3	1.6
1995	268	132	118	13	5	261	7	2.61
1996	324	174	127	14	9	313	11	3.39
AV ± SD	257.75 ± 55.61	128 ± 33.56	115.75 ± 14.97	9 ± 5.23	4.5 ± 3.42	251.25 ± 52.29	6.5 ± 0.74	2.4 ± 0.78

Table No. 1b. Patient Profiles

Hereditary influence	Perennial	Seasonal	Allergens	No. of attacks per year requiring hospitalization	Approximate annual cost of treatment (in Rs.)	No. of days of stay when hospitalization	Average cost of treatment per hospitalization (in Rs.)	Different system of medicines tried	Desired to practice yoga
66% → +ve 44% → -ve	17% (Jan-Dec)	83% (Jul-Dec)	100% allergic to dust, pollen grains, food and strong order	60% → 3 – 4 times 20% 6 – 7 times 20% → 8 –10 times	65% → 3000-4000 35% → 7000-15000	40% → 2-3 days 40% → 7-10 days 20% → 15-30 days	40% → 500-600 40% → 4000-5000 20% → 12000 – 15000	49% → Allopathy & Ayurvedic 32% → Allopathy & Homoeopathy 19% → only Allopathy	*1 Yes → 50% * 2 No → 50%

*1 → To minimize mediation
Maintain good health
Participate actively in all activities

*2 → Lack of confidence to do
Not interested

Table 2a. Peak expiratory flow rate (PEFR) readings using peak flow meter of volunteers during Yogasana Training

No.	Days	Avg ± SD	
		Before Yoga	After Yoga
1	1st day	400 ± 95.74	441 ± 93.17
2	4th day	407 ± 84.79	444 ± 80.18
3	7th day	403 ± 104.08	461 ± 100.08
4	10th day	400 ± 85.24	446 ± 101.91
5	14th day	406 ± 82.87	458 ± 80.35
6	17th day	424 ± 66.29	464 ± 70.20
7	21st day	421 ± 74.48	480 ± 59.72
8	24th day	418 ± 73.33	465 ± 78.83
9	27th day	455 ± 64.25	488 ± 54.90
10	30th day	458 ± 65.83	520 ± 62.29

*Values are Avg ± SD.

Table 2b. Influence of Yogasana Training on the Physiological parameters of Bronchial asthma patients

Days	Pulse rate (per min)	Respiratory rate (per min)	Breath holding time		Chest expansion (in cms)
			Exp.	Insp.	
Initial day	71.29 ± 3.90	13.71 ± 1.70	19.57 ± 7.2	38.14 ± 12.7	There is no change observed in chest expansion during the practice.
Final day	74.71 ± 4.27	10.7 ± 1.49	22.14 ± 7.45	45.74 ± 10.31	

Table 3. Medication profile before and during the practice of yogasanas

Sl.No.	Volunteer	Before the practice of yogasanas	During the practice of yogasanas
1	A	Tablets: Asthalin 2 mg, Betnesol, Deriphylline retard 300 mg, Actifed. Injection : Deriphylline, Aminophylline Aerosols : Asthalin, Serobid, Becoride, Pulmicort	No medication
2	B	Tablets : Asthalin 4 mg Aerosol : Asthalin	No medication
3	C	Tablets : Asthalin 2 mg, Theophylline 200 mg, Prednisolone 5 mg, Alprazolam, Bromohexine, Oximetazoline – HCl, Xylometazoline – HCl	No medication
4	D	Tablets : Polaramine, Isosalbetol, Celestone, Bricarex	No medication
5	E	Tablets: Asthalin 2 mg, Deriphyline retard 300 mg, Ayurvedic medicine which contains steroids.	No medication
6	F	Tablet : Asthalin 2 mg, Capsules: Broncap.	No medication

Table 4-Theophylline Pharmacokinetics Parameters

No.	C_{max} (μg/ml)	T_{max} (hours)	Elimination rate constant (k)	Biological half-life ($t_{½}$)	AUC (0-24)	AUC (0-∞)
Yoga Group						
A	15.8	4	1.06	0.654	198.1	201.31
B	12.6	6	1.02	0.692	174.2	177.32
C	8.6	6	0.599	1.16	101.9	105.91
D	4.4	3	0.986	0.703	65.0	67.03
E	22.0	6	1.21	0.573	258.9	260.55
F	48.0	10	0.461	1.50	349.1	373.83
Avg + SD	18.5 + 15.63	5.83 + 2.40	0.889 + 0.369	0.88 + 0.369	191.2 + 103.69	197.66 + 110.36
Non-Yoga						
G	12.6	3	0.191	3.63	92.7	107.36
H	29.2	8	2.59	0.268	323.3	324.77
I	14.0	8	0.247	3.43	194.2	197.1
J	12.6	8	0.092	7.52	177.3	227.3
K	6.2	8	0.276	2.51	51.5	55.12
Avg + SD	14.92 + 8.54	7.0 + 2.24	0.679 + 1.07	3.47 + 2.63	167.8 + 105.04	182.33 + 105.28

Discussion

In the present study an increasing trend in the prevalence rate of hospitalized patients was observed over a period of 4 years (Table la). Hospital necessity for children is noticed to be marginal, might be indication of parents concern in exercising medicatory in children's disease getting better. The perennial fraction of bronchial asthmatics is nearly 5 times less than the seasonal type. Extrinsic component exacerbating the disease is noticed in all of the patients. Data clearly indicates that the cost of the treatment cannot be afforded in the developing countries like India.

Patient education and counseling can play a major role in the effective disease management through naturopathy and yoga practice. Better disease management can be cost effective Dermatological and cosmetic application routes have been reported for NLC since they were originally described, but other routes related to SLN can also be used with this carrier system. Potential applications are discussed below.

9.1. Parenteral

SLN are generally injected intravenously, intramuscularly or subcutaneously. Because of their particle size below 1 flm, SLN formulations can be used for systemic body distribution with a minimal risk of blood clotting and aggregation leading to embolism. The particle size of an intravenously administered drug must be below 5 flm to avoid blocking of fine capillaries leading to embolism. Because of the physical and chemical instability of some molecules such as proteins, oligonucleotides and DNA in the gastrointestinal tract, they must be administered parenterally (Almeida *et al.,* 1997; Dass 2002; Hu *et al.,* 2004).

Also SLN provide a sustained release depot of the drug when administered subcutaneously or accumulated in the mononuclear phagocytic system (Wissing *et al.,* 2004). The drug is gradually released by erosion (e.g. degradation by enzymes) or by diffusion from the particles. Targeting a drug to the disease location is possible with SLN. For instance, targeting an anticancer drug is a distinctive feature of most studies, the aim being to convey a sufficient dose of drug to the tumor. SLN increase the tumour accumulation (Chen *et al.,* 2001), antibacterial activity (Bargoni *et al.,* 2001) of antiparasitic and antifungal drugs, and allow brain (economical). From table 2a it is evident that the yogasanas have a great impact on the physiology and therapeutic benefits in bronchial asthma patients. The significant increase in the peak expiratory flow rate (PEFR) is a measure of enhanced lung function, which is desirable in the better management of bronchial asthma. From Table 2b ventilation parameters such as respiratory rate, breath-holding time also has improved. From Table 3 it is evident that the practice of regular of yogasanas keeps one free from getting the attacks, and it can manage with chronic problem without any drug. Yoga thereby has a competitive edge over a pharmacotherapy in the cost effective management of bronchial asthma. It offers a blissful, better and healthy living to patients of asthma, a disease with social stigma, attached to it. From Table 4 the time to attain maximum concentration (Cmax) in saliva, time was formed to be 6 hours in yoga group, where as it is 8 hours in non-yoga group. The Cmax observed was 15.0 mg/ml and 12.9 mg/ml in yoga and non-yoga groups respectively. The area under the log saliva concentration and time curve from 0 to infinity for yoga and non-yoga groups was observed to be 189.69 and 171.56 respectively. The biological half-life (t1/2) observed to be more in non-yoga (3.48) than the yoga group (i.e., 0.918). The drug showed enhanced bioavailability in volunteers practicing yogasanas as compared to the patients who did not practice yogasanas. From the above data it can be concluded that the practice of yogasanas has significant effect on the pharmacokinetics of theophylline.

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