DOI 10.5935/0034-7280.20150071

Drop volume of artificial tear solutions: pharmacoeconomic study

Volume da gota dos colírios lubrificantes: estudo farmacoeconômico

Alexandre Xavier da Costa[1], Robson Miranda da Gama[2], Silvia Prado Smit Kitadai[3], Eric Pinheiro de Andrade[3], Gabriela Boia Rocha Ferro[4], José Álvaro Pereira Gomes[5]

ABSTRACT

Objective: To determine the mean drop volume produced by artificial tear solutions in different inclination angles and to determine the mean cost of the treatment. **Methods:** The drop volume of 3 original bottles of the artificial tear solutions *Artelac®*, *Hylo Comod®*, *Lacrima® Plus*, *Systane® UL*, *Lacrifilm®*, *Hyabak®*, *Lacribell®*, *Ecofilm®*, *Mirugell®*, *Plenigell®*, *Fresh Tears®*, *Optive®* and *Endura®* were determined at the inclination of 90º and 45º. The mean number of drops in each bottle was determined and a pharmacoeconomic evaluation of the drops was made. **Results:** The drop volume ranged from 32.2 to 64.0 µL at 45º and from 29.1 to 65.1 µL at 90º. The difference between drops in each inclination varied from 2 to 24%. The annual cost was from R$2,73 to R$130,73 according to the inclination of the bottle. The Maximum Duration of Treatment (MDT) was from 29.3 to 51.4 days at 45º and from 28.8 to 48.4 days at 90º, being the difference in MDT from 0.5 to 8 more or less days depending on each brand. **Conclusion:** None of the collyria studied presented ideal drops for human eyes, leading to a waste of the product and higher cost for the manufacturer and the consumer. We noted that there is a significant variation in the drop volume according to the inclination of the bottle, and that a variation of over 10% would bring financial impact for the patient.

Keywords: Ophthalmic solutions/administration & dosage; Ophthalmic solutions/economic; Medications instillation; Lubricant eyedrops; Pharmacoeconomics

RESUMO

Objetivo: Determinar o volume médio das gotas produzidas pelos colírios lubrificantes em diferentes ângulos de inclinação e determinar o custo médio do tratamento. **Métodos:** Determinação do volume da gota de 3 frascos originais dos colírios lubrificantes *Artelac®, Hylo Comod®, Lacrima® Plus, Systane® UL, Lacrifilm®, Hyabak®, Lacribell®, Ecofilm®, Mirugell®, Plenigell®, Fresh Tears®, Optive® e Endura®* à inclinação de 90º e 45º. Determinou-se o número médio de gotas em cada frasco e foi feita avaliação farmacoeconômica dos colírios. **Resultados:** O volume das gotas variou de 32,2 a 64,0 µL a 45º e de 29,1 a 65,1 µL a 90º. A diferença entre as gotas em cada inclinação foi de 2 a 24% e o custo anual dos colírios de acordo com a inclinação variou de R$2,73 a R$130,73. A Duração Máxima de Tratamento (DMT) foi de 29,3 a 51,4 dias na inclinação de 45º, e de 28,8 a 48,4 dias a 90º, sendo que a diferença na DMT foi de 0,5 até 8 dias a mais ou a menos, de acordo com a marca. **Conclusão:** Nenhum dos colírios estudados apresentou gotas ideais para o olho humano, levando a um desperdício do produto e maior custo para o fabricante e para o consumidor. Percebemos que existe uma variação significativa no volume da gota de acordo com a inclinação do frasco, e que uma variação maior do que 10% traria impactos financeiros para o paciente.

Descritores: Soluções oftálmicas/administração & dosagem; Soluções oftálmicas/economia; Instilação de medicamentos; Lubrificantes oftálmicos; Farmacoeconomia

[1,4,5]Escola Paulista de Medicina da Universidade Federal de São Paulo (SP), Brasil;
[2,3]Universidade de Santo Amaro – São Paulo (SP), Brasil.

Work done at the Semi-Industrial Lab School of Pharmacy of the University of Santo Amaro (UNISA) - (SP), Brazil.

The authors declare no conflicts of interest.

Received for publication 31/05/2015 - Accepted for publication 09/08/2015

Introduction

In the ophthalmic practice, the main route of drug administration is made by eyedrops. The official medical eyedropper, according to the American Pharmacopoeia, presents an outter diameter of 3 mm and dispenses 20 drops of distilled water per mL at a temperature of 25°C by positioning the eyedropper perpendicular to the person that will receive the drop[1].

The maximum capacity of the conjunctival sac in humans is approximately 30 µL. Thus, a drop of larger volume applied to a human eye will have its excess overflowed through the face and drained by the lacrimal pathways[2].

Whereas the basal tear secretion is approximately 7 µL, it was determined that the optimum concentration of a drug in the tear film is obtained with a droplet volume of around 20 µL, since smaller volumes might require increases in the concentration of the drug to ensure the same effectiveness. The optimal volume of a drop to be used in eyedrops would be of 20 to 23 µL to achieve the maximum use of the drug with the minimum waste possible[2].

Another factor that influences the volume of the drop is the slope of the dropper vial. According to the shape of the tip of the stopper and the surface tension of the liquid, there is a tendency of each vial producing a bigger or smaller drop when tilted than when it is inverted at 90°.

The present work aims at determining the average volume of the droplets produced by the vials of tear solution available in the Brazilian market when reversed at 90° and tilted at 45°, and determining the average cost of the treatment.

Methods

The research consists of a study of laboratory experimentation conducted in LESIFAR - Semi-Industrial Lab School of Pharmacy of the Pharmacy Course at the University of Santo Amaro (UNISA), in São Paulo - SP.

Three original vials were tested from 13 brands of tear solution: *Artelac® (Bausch & Lomb®); Hylo Comod® (Pfizer®); Lacrima® Plus and Systane® UL (Alcon®); Lacrifilm® and Hyabak® (Genom®); Lacribell®, Ecofilm®, Mirugell® and Plenigell® (Latinofarma®); Fresh Tears®, Optive® and Endura® (Allergan®).* We used the highest volume presentation available of the brands studied: 15 mL vials of the brands *Lacrima® Plus, Systane® UL, Lacrifilm®, Lacribell®, Ecofilm®, Mirugell®, Plenigell®, Fresh Tears®, Optive® and Endura®;* and 10 mL vials of the brands *Artelac®, Hylo Comod®* and *Hyabak®*. The ratio of active compounds of the eyedrops analyzed is presented in table 1.

The densitometry method for determining the volume was used to determine the volume of the drop[3-6]. We used the analytical scale Ohaus® Adventurer Pro AV264P (precision of 0.0001 and capacity of 240 g) with certificate of calibration, Laborglas® volumetric pipette of 1.0 mL and Laborglas® watch glass to determine the mass of the liquids.

The eyedrops were open at the time of test, and the weighing of drops was held by the same researcher, being filed the batch of each vial.

The mass of 10 drops from each vial of the samples analised was determined at room temperature (20 ± 2°C), first with the vial at 90° and then at a tilt of 45°. Each vial of eyedrops was lightly pressed until a drop fell off from a height of 5.0 cm from the watch glass used on the scale, and the process was repeated until the cumulative total of 10 drops studied was reached. For proper tilt, a protractor was used as a guide in a reference plane, and in relation to the vial base[3,6].

Table 1

Ratio of active compounds of the eyedrops analyzed

Product	Atcive compound
Artelac®	Hypromellose 3.2 mg/mL
Hylo Comod®	Sodium Hyaluronate 1 mg/mL
Lacrima® Plus	Dextran 1 mg/ml, Hypromellose 3 mg/ml
Systane® UL	Hydroxypropyl guar 8A, Polyethylene glycol 400
Lacrifilm®	Sodium carboxymethylcellulose 5 mg/ml
Hyabak®	Sodium Hyaluronate 1,5 mg/mL
Lacribell®	Dextran 70 1 mg/ml, Hypromellose 3 mg/ml
Ecofilm®	Sodium carboxymethylcellulose 5 mg/ml
Plenigell®	Sodium carboxymethyl cellulose, Glycerol
Mirugell®	Polyethylene glycol 400, propylene glycol
Fresh Tears®	Sodium carboxymethylcellulose 5 mg/ml
Optive®	Sodium carboxymethylcellulose 5 mg/ml, Glycerin 9 mg/ml
Endura®	Glycerin, Polysorbate 80, Castor Oil

Later, the mass of 1.0 ml of each eyedrop was measured with a volumetric pipette. This way, the average volume of each droplet was determined by the ratio between the mass of 1.0 ml and the weight of 10 drops of each eyedrop (volume-to-weight ratio)[3,6].

Te average number of droplets contained in each vial was also determined, taking into account the average volume of each drop and the total volume of the vial as advertised by the manufacturer on the product label[3-6].

Considering the dosage of 1 drop in each eye four times a day, for a total of 8 drops a day, the average cost of the drop, the monthly and the annual cost of the treatment were estimated according to the wholesale price, which is the highest price at which a laboratory or distributor of medicines can sell their product in the Brazilian market. This way, the wholesale price is the maximum allowable price for sales of medicines intended for pharmacies, drugstores, and Government entities. The prices of the medications analyzed are in Reais and with ICMS (Services and Merchandise Circulation Tax) of 18% (for the State of São Paulo), and were obtained by the Drug Market Regulation Chamber (CMED) of the Brazilian Sanitary Surveillance Agency (ANVISA), update on July 19, 2013[7].

It was decided not to use the Maximum Consumer Price[7], since some of the eyedrops have the status of Free from Taxation.

According to the average number of droplets contained in each vial and the dosage defined, it was also determined the Maximum Treatment Duration for each eyedrop, as well as the number of vials consumed per year.

Results

For the analysis of the results, the products were selected and randomly numbered for the definition of the sequence of data collection.

Table 2 presents the results of the mass of 10 drops and 1 milliliter drop volume, the volume of the droplet formed, the volume of the largest presentation found in market for each brand, and the wholesale price of the eyedrops analyzed under different tilt angles of the bottle during application.

Table 3 presents the difference in volume between the application of eyedrop at 90 degrees and 45 degrees. The average number of drops per vial was determined by dividing the volume announced by the manufacturer (for the presentation of bigger content) by the average volume of each drop, also obtaining the difference of the number of droplets formed per vial according to the tilt.

The results show that there is a trickle pattern between the different vials studied, since the volume of the droplets ranged from 32.2 to 64.0 μL at 45° and from 29.1 to 65.1 μL at 90°. The difference between the droplets in every tilt ranged between 2 and 24%.

The marks 1, 2 and 9 showed the droplet formed at 45° greater than the droplet formed with the vial inverted at 90°. In the other brands, the droplet formed at 90° was bigger (Graph 1). Note that the percentage of the difference in the volume of the droplet is roughly the same as the difference in the number of droplets. However, with the sign reversed, the bigger the drop the smaller number of droplets contained in vials will be, increasing the final cost to the consumer.

Table 4 presents the average cost per droplet of each eyedrop and the difference in price between the two different tilts, as well as monthly and annual average cost for a treatment defined as 1 droplet in each eye four times a day, with a total of 8 droplets per day.

The Maximum Treatment Duration ranged from 29.3 to 51.4 days on a 45° tilt and from 28.8 to 48.4 days at 90°, and the difference in the Maximum Treatment Duration was from 0.5 day to 8 days more or less according to each brand (Table 5).

We also calculated the average number of vials consumed per year if droplets are applied at 45° or 90°, and the difference in the number of vials which should be acquired by the patient each year (Table 6).

It was observed that a variation greater than 10% in the number of droplets in a vial according to the tilt of application indicates an increase in the number of vials consumed in a year, since for eyedrops 3, 5, 7, 8 and 10 (which have a variation in the number of droplets of less than 10%) there was no increase in the number of vials used in the period of 1 year.

Table 2

Results of mean values and standard deviation of the mass for 10 drops, 1 mililiter and the volume of the drop, volume of presentation and wholesale price of the eyedrops analyzed

	Mass in 10 drops (g)		Mass in 1mL (g)	Volume in1 droplet (mL)		Presentation (mL)	Price (R$)
Product	45°	90°		45°	90°		
1	0.3201± 0.0065	0.2641± 0.0114	0.9100 ± 0.0415	0.0353 ± 0.0018	0.0291 ± 0.0025	10	10,78
2	0.3147± 0.0346	0.2992± 0.0079	0.9772 ± 0.0140	0.0322 ± 0.0034	0.0306 ± 0.0011	10	not avaiable
3	0.6124± 0.0259	0.6234± 0.0742	0.9565 ± 0.0075	0.0640 ± 0.0023	0.0651 ± 0.0075	15	12,42
4	0.3723± 0.0139	0.4300± 0.0130	0.9706 ± 0.0071	0.0384 ± 0.0017	0.0443 ± 0.0015	15	32,65
5	0.3588± 0.0060	0.3811± 0.0154	0.9839 ± 0.0173	0.0365 ± 0.0012	0.0387 ± 0.0014	15	15,92
6	0.4143± 0.0493	0.4688± 0.0834	0.9386 ± 0.0240	0.0441 ± 0.0051	0.0500 ± 0.0090	15	10,47
7	0.4101± 0.0189	0.4390± 0.0187	0.9628 ± 0.0065	0.0426 ± 0.0017	0.0456 ± 0.0022	15	29,21
8	0.3561± 0.0078	0.3782± 0.0092	0.9648 ± 0.0121	0.0369 ± 0.0012	0.0392 ± 0.0011	15	39,17
9	0.3844± 0.0105	0.3226± 0.0155	0.9610 ± 0.0027	0.0400 ± 0.0010	0.0336 ± 0.0016	10	38,82
10	0.3537± 0.0056	0.3863± 0.0092	0.9660 ± 0.0034	0.0366 ± 0.0006	0.0400 ± 0.0011	15	30,92
11	0.4782± 0.0049	0.5895± 0.0039	0.9865 ± 0.0067	0.0485 ± 0.0002	0.0598 ± 0.0002	15	35,22
12	0.4649± 0.0099	0.6079± 0.0044	0.9424 ± 0.0116	0.0493 ± 0.0016	0.0645 ± 0.0006	15	44,29
13	0.3879± 0.0081	0.4484± 0.0113	0.9423 ± 0.0041	0.0412 ± 0.0009	0.0476 ± 0.0011	15	40,5

Table 3

Average volume of each drop in microlitres and the volumetric difference between every tilt, average number of droplets contained in each vial and the difference in the number of droplets formed in every tilt during

Product	Volume in 1 drpolet (μL)		Difference in the volume of drpolet between 90° and 45°		Number of droplet per vail		Difference of number of droplet per vail between 90° and 45°	
	45°	90°			45°	90°		
1	35.3	29.1	6.12	(21%)	283.66	343.28	59.63	(17%)
2	32.2	30.6	1.56	(5%)	310.64	326.50	15.87	(5%)
3	64.0	65.1	1.13	(2%)	234.34	230.28	4.07	(2%)
4	38.4	44.3	5.94	(13%)	390.96	338.57	52.40	(15%)
5	36.5	38.7	2.24	(6%)	411.07	387.26	23.81	(6%)
6	44.1	50.0	5.85	(12%)	339.93	300.16	39.77	(13%)
7	42.6	45.6	3.03	(7%)	352.27	328.84	23.42	(7%)
8	36.9	39.2	2.29	(6%)	406.29	382.55	23.74	(6%)
9	40.0	33.6	6.43	(19%)	249.99	297.84	47.85	(16%)
10	36.6	40.0	3.38	(8%)	409.65	375.06	34.59	(9%)
11	48.5	59.8	11.28	(19%)	309.44	251.02	58.42	(23%)
12	49.3	64.5	15.16	(24%)	303.97	232.53	71.45	(31%)
13	41.2	47.6	6.42	(13%)	364.35	315.23	49.13	(16%)

Graph 1

Difference in the volume of the droplet of each eyedrop (μL) according to their tilt

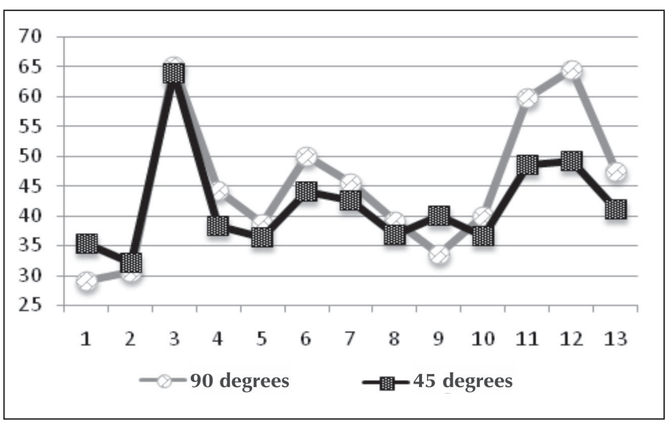

Table 4

Cost per droplet and their difference at 90° and 45°, and the monthly and annual cost for the treatment

Product	Cost of the droplet(R$)		Monthly cost (R$)*		Annual cost (R$)*	
	45°	90°	45°	90°	45°	90°
1	0.038	0.031	9.12	7.54	110.97	91.70
3	0.053	0.054	12.72	12.94	154.76	157.49
4	0.084	0.096	20.04	23.14	243.85	281.59
5	0.039	0.041	9.29	9.87	113.09	120.04
6	0.031	0.035	7.39	8.37	89.94	101.85
7	0.083	0.089	19.90	21.32	242.13	259.37
8	0.096	0.102	23.14	24.57	281.51	298.98
9	0.155	0.130	37.27	31.28	453.44	380.59
10	0.075	0.082	18.11	19.79	220.40	240.73
11	0.114	0.140	27.32	33.67	332.35	409.70
12	0.146	0.190	34.97	45.71	425.45	556.18
13	0.111	0.128	26.68	30.84	324.58	375.16

(*) For the dosage of 1 droplet in each eye 4 times a day

Table 5

Maximum Treatment Duration

Product	Maximum treatment duration*(dias) 45°	90°	Difference
1	35.5	42.9	7.5
2	38.8	40.8	2.0
3	29.3	28.8	0.5
4	48.9	42.3	6.5
5	51.4	48.4	3.0
6	42.5	37.5	5.0
7	44.0	41.1	2.9
8	50.8	47.8	3.0
9	31.2	37.2	6.0
10	51.2	46.9	4.3
11	38.7	31.4	7.3
12	38.0	29.1	8.9
13	45.5	39.4	6.1

*For the dosage of 1 droplet in each eye 4 times a day

Table 6

Number of vials a year

Product	Number of vails* 45°	90°	Difference
1	11	9	2
2	10	9	1
3	13	13	0
4	8	9	1
5	8	8	0
6	9	10	1
7	9	9	0
8	8	8	0
9	12	10	2
10	8	8	0
11	10	12	2
12	10	13	3
13	8	10	2

*For the dosage of 1 droplet in each eye 4 times a day

Discussion

The 5th Edition of the Brazilian Pharmacopeia published in 2010 is the Official Pharmaceutical Code followed in Brazil, and sets the standards and specifications of pharmaceutical, medications and other products subject to sanitary surveillance.

In the previous edition, the Brazilian Pharmacopeia defined that any measurement tool to administer liquid medicines must meet specific volumetric standards: the droplets should be counted in a normal dropper, which must provide a flow tube with 3 mm of outer diameter and 0.6 mm of internal diameter, ending in a tubular section. Twenty droplets of distilled water counted in the normal dropper at a temperature of 15°C must weigh 1g[8]. As 1g of distilled water corresponds to 1 mL, the volume of each droplet would have the volume of 50 µl, the measure mentioned by some authors as the maximum value allowed by the Ministry of Health for the volume of droplets of eyedrops[3,9], being 'eyedrop' defined as the pharmaceutical liquid preparation intended for application on the ocular mucosa[10]. As the eyedrop is instilled in the form of droplets, it must follow the specifications defined by ANVISA to administer liquid medications. However, note that the current legislation does not bring the definition of determination of the droplet volume anymore, nor sets specific regulations for the droplet volume of eyedrops. The eyedrops are a class of medication that deserves special attention, as there is a maximum volume tolerated by the eye of approximately 30 µL[2].

Besides that, in relation to the vial tilt, we found out that there is significant variation in the droplet volume, and there is a concern by manufacturers on this fact, since the directions of 12 out of the 13 brands tested fail to inform the consumer the correct way of instilling the eyedrop.

The American Pharmacopoeia (used as the main reference for Brazilian law) states that we must take into consideration that each substance has different characteristics, therefore the droplet size of each preparation will vary and, when the accuracy of each droplet is important (as in the case of eyedrops), the doser should be calibrated specifically for each preparation, assuming a variation of up to 15% in the volume of the droplet for each solution[1]. However, our analysis suggests that a variation above 10% in the volume of the droplet already bring financial impact to the consumer, since only for eyedrops 3, 5, 7, 8 and 10 (which have a variation in the number of droplets of less than 10%) there was no increase in the number of vials used in the period of 1 year.

The dosage used in this study for tear solutions was based on the way we usually prescribe these eyedrops in our service, also considering the fact that eyedrops with preservatives should not be used more frequently than 4 times a day, so that there is no damage to the eye surface. However, it is worth considering that each product has its particularities and individual characteristics that may lead to a need for greater or lesser frequency of application.

We are concerned that neither the Brazilian nor the American Pharmacopoeia considers the eye continent limit for the production of eyedrops, and we understand that more attention should be given to the production of droplets of smaller volume, so there is no waste or risk of increased systemic absorption of some drug.

The concept of pharmacoeconomics is growing nowadays, and concerns the application of the principles of economics to the study of medications and health practices, aiming at the optimization in the use of financial resources without prejudice to quality and treatment outcomes[11].

Considering the therapeutic equivalence of tear solutions, the cost minimization analysis is a simple way of economic evaluation in which only the costs are subjected to comparisons because the efficacy or the effectiveness of the comparable alternatives are equal[11,12].

Therefore, we realized that the droplet volume of eyedrop is still considerably high, and that this leads to a waste of the product and increased cost to the manufacturer and the consumer. Once the adjustment of the stopper to calibrate smaller droplets is a costly process, an immediate action to minimize the cost would be properly guide the consumers in a descriptive and illustrative way in the directions of which would be the best way of applying each eyedrop.

Conclusion

None of the eyedrop vials studied showed droplets ideal to the human eye, leading to product waste and increased cost to the manufacturer and the consumer. We noticed that there is a significant variation in droplet volume according to the vial tilt, and that a variation greater than 10% would bring financial impact for the patient.

Further studies should be conducted with other classes of eyedrops, and we must worry each time more about the droplet volume of eyedrop, so that an ideal is reached.

References

1. United States Pharmacopeia 30, National Formulary 25 (USP-30 NF 25). Pharmaceutical Dosage Forms. USA: The United States Pharmacopeial Convention; 2007. p. 584.
2. Galvão-Neto P, Rocha Júnior FS, Ribeiro BB, Silva FA, Figueiredo CR, Batista WD. Volume da gota dos análogos das prostaglandinas. Rev Bras Oftalmol. 2004; 63(9-10):457-62.
3. Estacia P, Tognon T. Considerações sobre o ângulo de administração de colírios antiglaucomatosos análogos das prostaglandinas. Arq Bras Oftalmol. 2008;71(5):684-8.
4. Gaynes BI, Singa RM, Cao Y. Dosage variability of topical ocular hypotensive products: a densitometric assessment. J Glaucoma. 2009;18(2):149-52.
5. Gaynes BI, Singa RM, Schaab G, Sorokin Y. Impact of administration angle on the cost of artificial tear solutions: does bottle positioning minimize wastage? J Ocul Pharmacol Ther. 2007;23(2):196-201.
6. Prata-Jr JA, Prata JA. Comparação do volume da gota e custo do tratamento dos genéricos de maleato de timolol 0,5%. Arq Bras Oftalmol. 2004;67(3):419-22.
7. BRASIL. Agência Nacional de Vigilância Sanitária. Câmara de Regulação do Mercado de Medicamentos. [citado 2013 Out 23]. Disponível em: http://portal.anvisa.gov.br
8. Farmacopeia Brasileira. 3a ed. Brasília (DF): ANVISA; 1977.
9. Roizenblatt R, Freitas D, Belfort Jr R, Hofling-Lima AL, Prata Jr JA. Impacto econômico no tratamento do glaucoma: volume de gotas de colírios antiglaucomatosos brasileiros e norte-americanos. Arq Bras Oftalmol. 2001; 64(2):143-6.

10. Farmacopeia Brasileira. 5a ed. Brasília (DF): Anvisa, 2010; vol.2, p.546.
11. Guimarães HP, Barbosa LM, Laranjeira LN, Avezum A. Estudos de farmacoeconomia e análises econômicas: conceitos básicos. Rev Bras Hipertens. 2007;14(4): 265-8.
12. Tonon LM, Tomo TT, Secoli SR. Farmacoeconomia: análise de uma perspectiva inovadora na prática clínica da enfermeira. Texto Contexto Enferm. 2008;17(1):177-82.

Corresponding author:
Alexandre Xavier da Costa
Rua Botucatu, 821- São Paulo, SP, Brazil
Telephone: 55 11 98205-5520
Email: dr.alexandre.x@gmail.com