The Effect of Haemodialysis on Serum Theophylline Level

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Abstract

Objective: The study was designed to investigate the effect of haemodialysis on serum theophylline levels (STL).

Materials and Methods: Nine patients diagnosed with chronic obstructive lung disease or bronchial asthma and who are already receiving theophylline treatment were included in the study (F:5, M:4). Their mean age and mean duration of haemodialysis were 51.2±6.8 years and 21.7±15.3 months respectively. Three patients were on 200 mg twice daily sustained release theophylline and 6 patients were receiving 300 mg twice daily. STLs were measured just before (11.00 am) and after (3.00 pm) the haemodialysis sessions. Three days later when the patients came for their routine haemodialysis sessions their session was deferred from 11.00 am to 3.00 pm and their STLs were measured at 11.00 pm and 3.00 pm (non-haemodialysis period).

Results: Just before and after the haemodialysis sessions, mean STL values were 10.5±1.8 mg/l and 6.2±1.5 mg/l respectively ($p<0.01$). Mean initial and final STL values in the non-haemodialysis period were 10.1±2.2 and 9.4±1.7 mg/l ($p>0.05$). During the haemodialysis session STL values fell to subtherapeutic levels in 8 out of 9 patients (88%). This drop occurred in 1 of 8 patients (12.5%) during non-haemodialysis session. Overall theophylline clearance rate by haemodialysis was calculated as 35%.

Conclusion: One session of haemodialysis lowered STL to sub-therapeutic levels in the majority of patients. We therefore suggest that the dosage of theophylline needs to be adjusted accordingly. This can be done either by increasing the dose taken just before the haemodialysis or by the infusion of some additional theophylline during the haemodialysis session.

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Introduction

Although theophylline has lost its popularity in the last 20 years, it still is an effective drug commonly prescribed in the management of bronchial asthma and chronic obstructive pulmonary disease (COPD) (1,2). Its narrow therapeutic range, wide individual variations in its elimination rate and side effects even at low serum theophylline levels (STL) led many clinicians to be reluctant in using theophylline preparations. The pharmacokinetics and elimination rate of theophylline are influenced by many factors and maintenance of adequate serum levels not infrequently necessitate readjustment of the dose (2-4).

Assuming that the prevalence of concomitant COPD and bronchial asthma in patients on chronic haemodialysis is not any smaller than that of the general population, it will not be a surprising finding that many of these patients are given

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Table 1. Clinical features of the patients

Patient no.	Age	Gender	Aetiology	Dialysis duration (months)
1	45	F	Pyelonephritis	30
2	40	M	Diabetes mellitus	36
3	50	F	Pyelonephritis	12
4	52	F	Diabetes mellitus	10
5	58	M	Unknown	8
6	60	F	Policystic kidney	4
7	55	M	Diabetes mellitus	36
8	45	F	Unknown	13
9	56	M	Diabetes mellitus	46

F: Female, M: Male

Table 2. Initial and final STL values (mg/dl) during haemodialysis and non-haemodialysis sessions

Patient no.	Haemodialysis session		Non-haemodialysis session	
	Initial	Final	Initial	Final
1	10.8	4.7	9.9	9.5
2	8.7	6.8	12.1	8.4
3	13.4	7.4	14.5	13
4	9.2	9	7.9	9.4
5	11.7	3.8	9.4	8.3
6	9.3	6.7	8.6	7.9
7	8.8	5.8	11.5	11
8	10.2	5.5	9	9.7
9	12.8	5.8	8.4	7.5

STL: Serum Theophylline Level

theophylline as part of their treatment. It can also be assumed that the adjustment of the theophylline dose will be particularly difficult in these patients, one reason being the accelerated clearance of theophylline from plasma by haemodialysis. Our knowledge about the effect of haemodialysis on plasma theophylline clearance is limited to a small number of isolated case reports of severe theophylline intoxication treated by haemodialysis (5-9) and to one uncontrolled clinical study (10).

This present study aims to clarify the effect of haemodialysis on clearance of theophylline from the plasma in patients with chronic renal failure (CRF).

Materials and Methods

The study was carried out at Malatya İnönü University, Turgut Özal Research Center, by the Departments of Pulmonary Medicine and Nephrology and a Private Haemodialysis Center, Malatya Doğu Kliniği, extending from January 1999 to February 2001. Of the 482 patients on chronic haemodialysis, 9 patients (F:5, M:4) utilising theophylline preparations were included in the study. The study protocol was approved by the ethics committee of the center and informed consent was obtained from the patients.

None of the patients had concomitant liver failure, heart failure or elevation of hepatic enzymes. Patients were already on theophylline for their bronchial asthma (n: 6) or COPD (n: 3). The first measurements of serum theophylline level (STL) were done following a period of two weeks during which the theophylline regimen was standardized and all patients were started on oral sustained release theophylline (Teokap sustained release 200 or 300 mg twice daily, micropellet capsule, Nobel Inc, Turkey) taken twice a day at 8.00 am and 8.00 pm, with a therapeutic dose interval adjusted to 8-15 mg/dl. The haemodialysis sessions were regulated to start at 11.00 am and end at 3.00 pm.

Cigarette smoking, tea and coffee drinking and chocolates were withheld for 24 hrs prior to the measurement of STL. Haemodialysis was performed using a Fresenius 4008-B (Berlin, Germany) dialyser using polysuflon F4-1.4 m^2 membranes with a blood flow rate of 300 ml/min for 4 hrs. Blood samples for STL determinations were taken immediately before and after a haemodialysis session. Three days later when the patients came for their routine haemodialysis, their session was deferred from 11.00 am to 3.00 pm and and blood samples were taken 11.00 pm and 3.00 pm (non-haemodialysis sessions) for measurement of STL. The theophylline clearance rate by haemodialysis (TCRH) was calculated by using this formula:

$$TCRH = [1-(\text{mean final } STL_{\text{first session}}/\text{mean initial } STL_{\text{first session}})] - [1-(\text{mean final } STL_{\text{non-haemodialysis session}}/\text{mean initial } STL_{\text{non-haemodialysis session}})] \times 100\%.$$

Wilcoxon's signed rank sum test was utilised for the statistical analyses. All values were presented as means and standard deviations. Any P value less than 0.05 was considered as statistically significant.

Results

Mean age of the patients was 51.2±6.8 years. Mean duration of the haemodialysis was 21.7±15.3 months. Clinical data on each patient is presented in Table 1. Mean STL values just before and after the haemodialysis session, were 10.5±1.8 mg/l and 6.2±1.5 mg/l respectively. STL was within the therapeutic range in all patients before the haemodialysis, but was within the therapeutic range after the haemodialysis in only one patient. When the patients were off dialysis, mean STL was 10.1±2.2 mg/l at 11.00 am and 9.4±1.7 mg/l

at 3.00 pm, and within the therapeutic range in 8 and 7 patients. The difference between initial and final STL values were statistically significant in the haemodialysis session ($p<0.01$), but essentially comparable in the non-haemodialysis session ($p>0.05$). STL values for each patient are presented in Table 2. By using the formula described above, TCHR was calculated as 35%.

Discussion

The results of our study show that haemodialysis remarkably accelerates the clearance of serum theophylline, and one session of haemodialysis decreases the STL value to sub-therapeutic levels in most of the patients.

Although the cellular mechanisms of theophylline action for its bronchodilatory effect have not yet been clearly understood, phosphodiesterase enzyme inhibition, adenosine antagonism and induction of cathecolamine release are the most popular mechanisms suggested (2-4,11,12). Apart from its bronchodilatory effect, theophylline is also thought to have an anti-inflammatory effect. Increasing mucociliary clearance, increasing diaphragmatic contractility, prostaglandin antagonism, stimulation of the respiratory center, stimulation of diuresis, increasing cardiac contractility, and decreasing pulmonary artery pressure are some other proposed effects of theophylline (4,12). Optimal therapeutic level for theophylline has also been a matter of debate for a long time. Initially, this level was accepted to be between 10-20 mg/dl (2,13). Since levels over 15 mg/dl were observed to be frequently toxic, a targeted therapeutic level between 5-15 mg/dl was subsequently proposed (3,4,14). Some researchers argued that serum levels less than 8 mg/dl could achieve only minimal bronchodilation effect, and that the therapeutic level should be between 8-12 mg/dl (15), but difficulties were encountered in the level to such a narrow range. More recently, it has been proposed that it would be easier to adjust the therapeutic level to 8-15 mg/dl (16). Considering all these arguments, we accept the therapeutic range as 8- 15 mg/dl in our study.

Because of the difficulties in designing a prospective study on theophylline clearance by haemodialysis, previous experience in this area is limited to isolated case reports of theophylline intoxication treated by haemodialysis (5-9). In theophylline intoxication cases, many researchers recommend that if STL is less than 60 mg/l, repeated administration of activated charcoal alone is enough (9,17). The justification of activated charcoal administration comes from the fact that oral bioavailability of theophylline is around 80-100%, and if we can just stop its intestinal absorption the intoxication usually abates in the mild cases (12). When STL reaches values between 60 mg/l and 100 mg/l, a combination of activated charcoal and peritoneal dialysis is recommended in the treatment (18). In more severe forms, haemodialysis in combination with activated charcoal administration should be the choice of treatment (19). The difference between peritoneal and haemodialysis is in their clearance rate. The clearance rate of theophylline by peritoneal dialysis is around 25% (9) and by haemodialysis between 28-79% (5,9,20) Depending on the blood flow (100 ml to 300 ml) through the dialysis machine, haemodialysis increases the clearance rate remarkably. There is no significant difference between the two procedures with regard to mortality and morbidity (9).

In our study the clearance rate by haemodialysis was 35%. More importantly, although oral sustained release theophylline preparations exert their activity for a period of 12-14 hrs with quite stable peak serum levels at 1 to 10 hrs after administration (12), haemodialysis led to a decrease in serum theophylline to sub-therapeutic levels in 8 of our 9 patients (88%). Considering the very low volume distribution and the low molecular weight (180 kilodalton) of theophylline, this finding of high dialysability of theophylline is not surprising for us (5,18,21).

Assuming that 5-10% of chronic haemodialysis patients have COPD or bronchial asthma, 1-2% of them can also be assumed to utilise theophylline preparations either continuously or intermittently. There is no doubt that the proper adjustment of theophylline maintenance dosage is particularly difficult with traditional dosing methods during the accelerated clearance period of haemodialysis in these patients. On the other hand, on the days when patients with CRF are not on haemodialysis and 80-90% of the theophylline is cleared by the liver, it is not necessary to interfere with the established maintenance dosage of the patients (12).

In conclusion, our study clearly demonstrated that in the majority of patients utilising theophylline, STL is decreased to subtherapeutic levels during haemodialysis by accelerated elimination. We therefore suggest that the dosage of theophylline needs to be adjusted accordingly. This can be done either by increasing the dose taken just before the haemodialysis or by the infusion of some additional theophylline during the haemodialysis session.

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