The utility of therapeutic drug monitoring was studied in children with apnea. Plasma levels of theophylline were monitored in 106 patients. Of these 106 patients, 19% had subtherapeutic levels (group 1), 60% had therapeutic levels (group 2), and 21% had toxic levels (group 3). After we adjusted dosages and instituted monitoring, theophylline levels for group 1 rose to 8.12 mcg/ml on average and levels in group 3 were 8.3 mcg/ml. Another group of children who were not monitored spent from 14 to 26 days in the hospital; the monitored patients spent from 9 to 19 days. We concluded that monitoring of theophylline levels is supportive for newborns with apnea.

Key words: apnea, breathing, children, drug monitoring, theophylline

INTRODUCTION

Several reports have indicated that therapeutic drug monitoring (TDM), when used appropriately and interpreted in the proper clinical and pharmacokinetic context, is an excellent instrument for individualizing dosages of many drugs and, consequently, for controlling theophylline levels.1 TDM, which is intended to maintain serum drug concentrations and the effects produced, is one of the main activities of clinical pharmacology that supports pediatric care services and allows physicians to administer the optimal therapy.2

Apnea is a common problem in newborn infants and contributes to increased morbidity and mortality in these age groups. It is defined as a cessation of breathing for 15 seconds or more, especially during sleep, and is often accompanied by bradycardia and cyanosis.3 A pause in respiration that lasts as long as 5 to 10 seconds and alternates with normal breathing is called periodic breathing.

Apnea can be complicated, because the frequency of heartbeats is significantly diminished and there is a potential for severe cerebral damage.

For several years, theophylline has been the drug of choice for the treatment of apnea in the preterm infants because of its bronchodilator effect.4 Although the use of caffeine has been recently introduced, some studies of premature neonates indicate that aminophylline and citrate caffeine are equally effective in preventing apnea and bradycardia.5

These conditions must be controlled because the loss of effective breathing can lead to hypoxemia and cerebral damage. Theophylline reduces the incidence of apnea and periodic breathing by stimulating ventilation, resulting in improved diaphragm potency in term infants with these respiratory abnormalities.5

The serum levels of theophylline recommended to prevent these episodes range from 3 to 10 mcg/ml, obtained by a dose of 2 to 4 mg/kg per day.7 Because of the narrow therapeutic index of this drug, monitoring its plasma concentration is essential and should be done until a steady state has been reached.8

In this article, we describe the results of therapeutic monitoring of theophylline in a group of children with apnea for whom TDM was indicated.

METHODS

We monitored the serum levels of theophylline in 106 patients with apnea, 55 girls and 51 boys, in the pediatric department of General Hospital of Mexico City. The mean weight of the children was 1.91 kg. The patients were given 1 mg/kg over eight hours of intravenous (IV) theophylline. Of the 106 patients, 24 were preterm infants (average age, 32 gestational weeks) and 82 were term infants (average postnatal age, 26 days) when TDM was initiated.

We performed the first TDM between the third and the fifth days of treatment, which is the time necessary for a steady state of theophylline to be achieved. Two hours after theophylline administration, 200 microliters of blood was drawn via a puncture of the infant’s heel using labeled capillaries containing heparin. After centrifugation, 50 microliters of plasma was taken to measure theophylline levels by enzyme-immunoassay technique (EMIT) (Syva-Dade Behring Diagnostic Products).

For patients whose plasma levels were out of therapeutic range in the first TDM, we performed a second and third TDM to evaluate its utility and to consider respective dosage adjustments based on drug levels and the adverse drug events (ADEs) observed. We adjusted dosages according to Ritschel’s method.9

RESULTS

We analyzed 106 samples from patients after the first TDM. Of these patients, 20 (19%) achieved subtherapeutic theophylline levels. Apnea was manifested in 11 patients, and nine infants were experiencing periodic breathing.

In 64 patients (60%), theophylline levels were in the therapeutic range and were clinically controlled without relevant

Hugo Juárez-Olguin is Chief of the Laboratorio de Farmacología at the Instituto Nacional de Pediatría and Professor of Pharmacology at Universidad Nacional Autónoma de México in Mexico City, Mexico. Janett Flores-Pérez is Associate Researcher at the Laboratorio de Farmacología and Professor of Pharmacology at the Universidad Nacional Autónoma de México. Gabriela Pérez-Guilé, Adrián Guillé-Pérez, Angélica Camacho-Vieyra, Carmen Flores-Pérez, and Mayra Jarillo-Alvarado are Associate Researchers at the Laboratorio de Farmacología.
effects. In 22 patients (21%), theophylline levels were considered toxic and 12 of the patients experienced tachycardia. The last 10 children had no clinical manifestations of apparent toxicity.

The children whose theophylline concentrations were out of therapeutic range were classified according to the results of the initial monitoring. In the follow-up evaluation, they were considered to be group 1 (n = 20), patients whose initial monitoring corresponded with subtherapeutic levels, with concentrations ranging from 0.48 to 2.90 mcg/ml. For this group, we suggested that the dose be increased, as Ritschel reported, with another round of TDM to be performed three days later.

During the second TDM, theophylline levels reached 8.12 mcg/ml; upon follow-up, the levels were at an average of 7.2 mcg/ml during the third TDM. During the second and third TDMs, theophylline levels were clinically controlled.

The monitoring results for group 1 are shown in Figure 1.

For group 2 (n = 64), which corresponded to the patients with therapeutic levels in the first TDM, we recommended maintaining the same dosage and interval because levels were clinically controlled.

Group 3 (n = 22) consisted of patients with toxic levels during the first TDM. For this group, plasma levels reached 30.2 mcg/ml. Some of these infants presented with tachycardia at a rate of 158 beats per minute. Elevated levels of theophylline prevailed in the preterm infants. We recommended suspending the treatment for 24 hours and continuing with the dose adjusted as for that in group 1. In the second and third TDMs, levels of 8.3 mcg/ml and 6.4 mcg/ml, respectively, were achieved. The theophylline levels in these patients were clinically controlled during the TDMs.

The monitoring results for group 3 are shown in Figure 2.

DISCUSSION

There was a wide variability in the serum levels, which ranged from 0.4 to 30.2 mcg/ml. Elevated levels were probably attributable to the inability of some patients to eliminate the drug.2

In the patients with subtherapeutic levels, serum concentrations were less than 3 mcg/ml, with a mean concentration of 1.5 mcg/ml; either apnea or periodic breathing was present. On the basis of our clinical experience and previous reports, we suggested increasing the dosage.10 In some patients, the breathing rate that physicians considered to be altered from the normal rate may have been an antecedent to a period of apnea and might be sufficient cause to adjust the dosage based on previous studies.10

For the second TDM three days later, theophylline levels showed a mean increase of 8.12 mcg/ml and were similar during the third TDM. Levels in these patients were reported to be clinically controlled.

In the group of patients with initial toxic levels, the mean serum levels were 22.8 mcg/ml, rising to 31.0 mcg/ml in one case. We recommended that treatment be discontinued for this group and that the dosage be adjusted with another round of TDM three days later. On the second and third TDMs, serum theophylline levels diminished and were clinically controlled.

For group 1, as with group 3, we performed TDM after three days had passed, when the new steady state had been
reached. Elevated serum levels prevailed in the preterm infants. Achieving clinical control of these children was difficult because two or three TDMs were necessary.

From the results of the patients analyzed, we noted the utility of TDM, principally for patients whose serum levels were out of therapeutic range at the first evaluation and who experienced ADEs. TDM is an important supportive measure for individualizing dosage regimens. However, with drugs such as theophylline, monitoring of drug levels is necessary only if patients exhibit clinical manifestations of ADEs.

We emphasize that TDM is more efficient if the responsible physician is always kept aware of developments. One purpose of this study was to demonstrate the utility of the correct usage of theophylline monitoring and to evaluate its role in hospital length of stay. After consulting the database of the pediatric department, we found that the duration of hospitalization for patients with recurrent apnea ranged from 12 to 28 days. The length of stay for the 106 patients studied decreased to 8 to 20 days, which means a savings in economical resources, because the cost of one day in the neonatology service is the highest in our hospital. Drug monitoring can bring down hospital costs by 30%, and it has proved useful in the medical field.

Acknowledgments. The authors thank all of the medical staff in the Department of Pediatrics at General Hospital of Mexico City, where this work originated, and to Dr. Isabel Pérez-Montfor for assisting with the writing.

REFERENCES