

Tolerability of doxofylline in the maintenance therapy of pediatric patients with bronchial asthma

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Abstract. – A retrospective open study was performed to ascertain the tolerability of doxofylline in pediatric patients with bronchial asthma or airway obstruction complicating acute bronchitis. The study population included 806 patients aged between 3 and 16 years. Doxofylline (200 mg sachets) was administered at daily doses ranging from 100 to 400 mg. The percentage of patients reporting side effects was 11%. The percent of patients reporting moderate side effect was 5%, the others being mild. The percent of patients reporting adverse event very likely due to doxofylline was 6%. The percent of patient drop-outs related to side effects was 5%.

Key Words:

Doxofylline, Bronchial asthma, Bronchodilator, Pediatric.

ty profile of the drug^{6,7}. Additionally, unlike theophylline, doxofylline did not antagonize calcium channel blocker receptors and did not interfere with the influx of calcium into the cells⁸.

Doxofylline was commercialized in Italy by the end of the 1980s. In 1990, the pediatric formulation was introduced. Over the first three years of post-marketing therapeutic use, an estimate of 10.000 pediatric patients were treated with doxofylline. Almost a decade has passed since the launch of the pediatric formulation. In this period, neither deaths nor major side effects related to the drug were reported to the Italian Ministry of Health⁹. However, since data from a large sample of pediatric patients were lacking, in the present study we sought to obtain more detailed information on therapeutic uses and tolerability of doxofylline in children with asthma and other pulmonary disease with a spastic bronchial component.

Introduction

Doxofylline ([7-(1,3-dioxolan-2-ylmethyl)theophylline] is a methylxanthine bronchodilator characterized by the presence of a dioxolane group in position.

Bronchodilator activities of doxofylline have been documented in animal studies¹⁻³ and in clinical trials involving patients with either bronchial asthma or chronic obstructive pulmonary disease^{4,5}.

Doxofylline activity is mediated, at least partly, by the inhibition of phosphodiesterase enzymes followed by the increase of intracellular concentrations of cyclic AMP that is likely to cause smooth muscle relaxation. Moreover, it has been suggested that decreased affinities toward adenosine A₁ and A₂ receptors may account for the better safe-

Patients and Methods

A phase-four open retrospective clinical study was performed on the therapeutic uses and tolerability of doxofylline. Data were collected from 102 physicians specialized in pediatrics, hospital pediatricians and pneumologists who treated patients of pediatric age with doxofylline. The drug was prescribed as 200 mg sachets and it was administered orally as solution. The recommended doses of doxofylline in maintenance therapy were: 6 mg per kg of body weight every 12 hours, in case of unsatisfactory response and under medical supervision it was possible to increase the

dose up to 9 mg per kg of body weight every 12 hours.

The evaluation criteria were based on the following items:

- therapeutic use,
- patient's age,
- dose regimen,
- concomitant medications,
- side effects,
- drop-outs,
- global evaluation of efficacy,
- global evaluation of tolerability.

Data from the study patients were collected on a case report form.

All the side effects were recorded during the study and they were classified as drug related in case they were possibly related, definitely related or unknown. Side effects were considered mild if the discontinuation of therapy was not needed, moderate if the patient had to stop the treatment and severe in case of hospitalization related to the drug.

The global efficacy of the drug was assessed according to a 4-grade scale: poor, modest, good and very good. The overall tolerability of the drug was based on the same 4-grade scale.

Table I. Summary of demographic data (range in brackets).

Doxofylline 200 mg	
Number of subjects	806
Age (years)	8 (3-16)
% of women	39%
Body weight (kg)	34 (14-85)
Hospitalization for asthma (%)	42%
Age at the onset of asthma	3 (1-16)
Years since onset	8 (1-15)
Precipitating factors (%)	95%

Results

We collected data from 806 patients treated with the pediatric formulation of doxofylline from 1991 through 1993. The study population was composed of 61% males and 39% females. The main therapeutic uses were: acute and chronic asthma (67%) and airway obstruction complicating acute bronchitis (30%).

The demographics of the study patients are summarized in Table I. The age of the patients ranged between 3 and 16 years (mean age: 8 years) (Table I, Figure 1). The daily doses of doxofylline varied from 100 mg to 400 mg (Figure 2). In reference to body weight, in most of the patients the dose

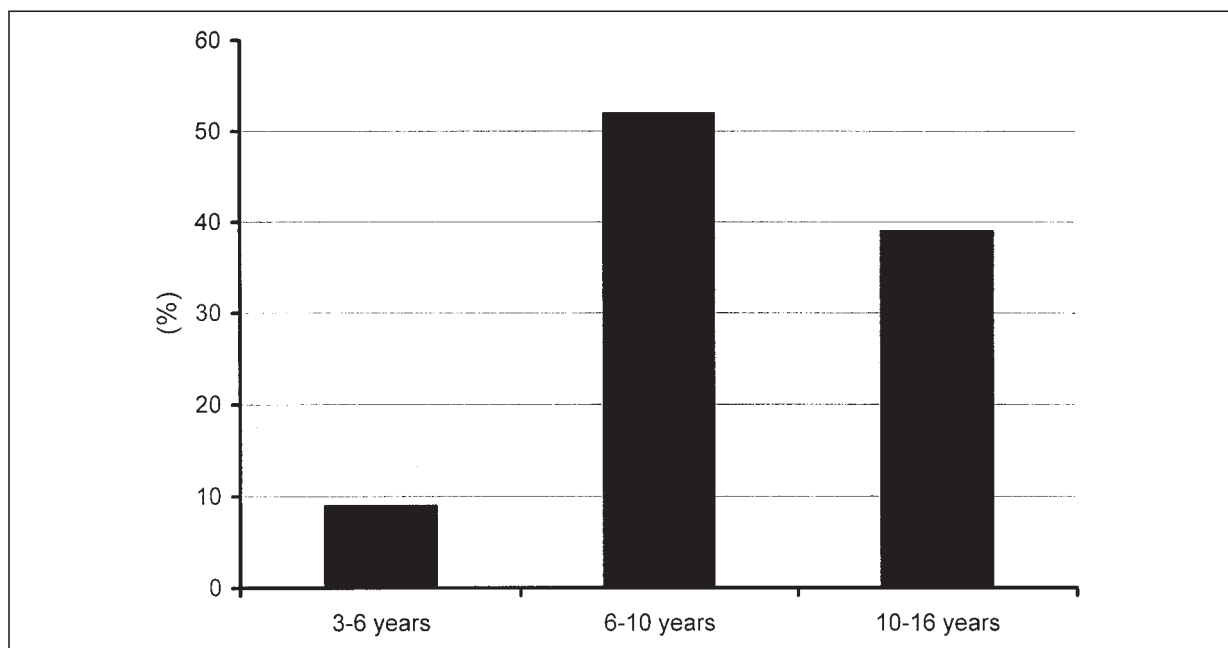


Figure 1. Study patients categorized according to their age.

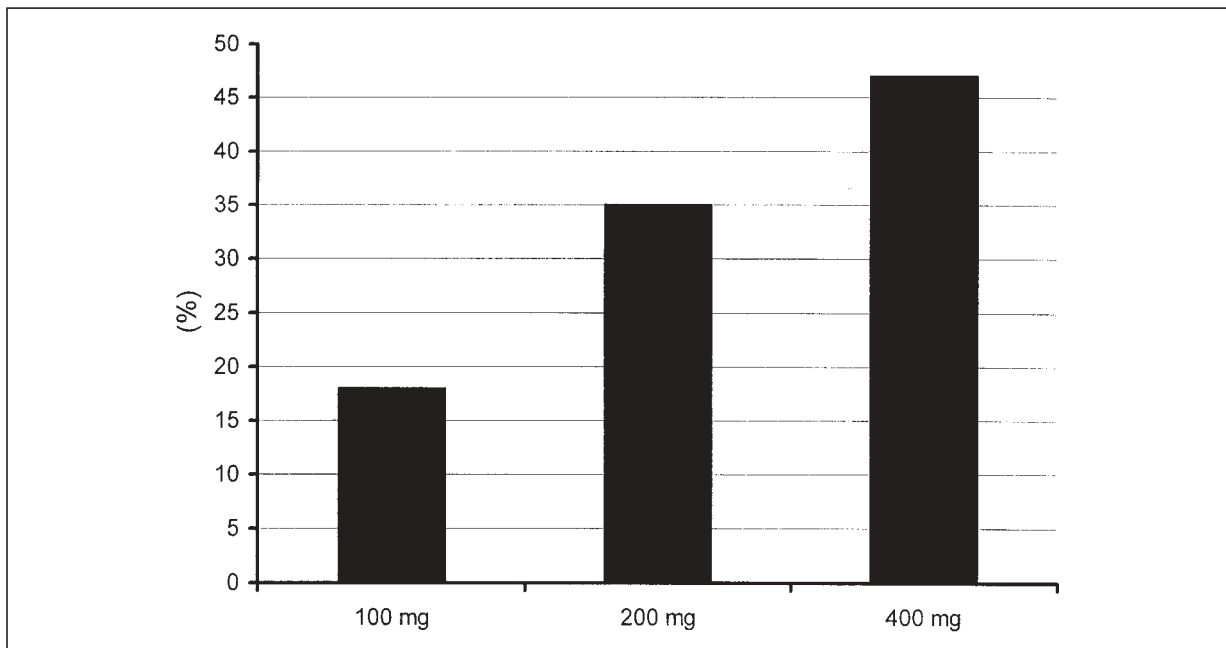


Figure 2. Dose regimen of doxofylline in the study population.

of the medication complied with the recommended regimen. The duration of therapy in the study patients is illustrated in Figure 3. Doxofylline was mostly administered in combination with other drugs (96%). Concomitant medications were beta-2-stimulant drugs (67%), mucolytics (39%), steroids (31%), antibiotics (45%), non-steroid anti-inflammatory drugs (5%) and others (8%). More than one-half of the patients received three or more drugs.

The percentage of patients reporting side effects was 11%. The percentage of patients reporting moderate side effects was 5%. The percentage of patients reporting definitely drug-related adverse events was 6%. The percentage of patient drop-outs related to side effects was 5%.

Concerning the side effects related to specific organs and systems, we were able to collect data from a subgroup of 430 patients. As shown in Table II, the vast majority of side effects concerned the gastro-intestinal system (76%), while few of them regarded the central nervous system (16%). The occurrence of palpitations was the only side effect attributable to the heart (9%).

Global evaluation of efficacy indicated more than a trend toward definite efficacy (good and very good: 62%). The tolerability

of the compound was judged as satisfactory in most of the cases (good and very good: 76%) (Figure 4).

Discussion

Bronchial asthma occurs at all ages but predominantly in early life. It has been indicated that 7 to 10 percent of children have bronchial asthma. About one-half of the cases develop before age 10¹⁰.

It is well known that theophylline may be of benefit in chronic management and maintenance therapy of asthma. The drug can be added to the patient's regimen if inhaled agents fail to control the disorder. However, the use of theophylline is frequently associated with the occurrence of side effects, i.e. nausea, vomiting, epigastric pain, insomnia, anxiety, restlessness, tachycardia and extrasistoles, which may limit its clinical use⁷. With the introduction of doxofylline, a newly derived xanthine drug with less extrapulmonary effects due to reduced affinity for adenosine receptors, it seemed possible to improve the tolerability of methylxanthines¹¹⁻¹³. Data from clinical trials confirmed that doxofylline was associated with

Table II. Side effects in the study population divided according to intensity and type in a subgroup of 430 patients.

	DEGREE OF SEVERITY		
	Total	Mild	Moderate
Gastrointestinal	33	15	18
Nausea	20	10	10
Vomiting	9	3	6
Epigastric pain	4	2	2
Nervous system	7	3	4
Headache	3	2	1
Insomnia	2	1	1
Dizziness	1	0	1
Tremor	1	0	1
Cardiovascular	3	3	0
Palpitations	3	3	0

less gastrointestinal, cardiac and central nervous system untoward effects¹⁴.

The results of clinical studies performed in adult patients with asthma showed that doxofylline was as effective as theophylline

while it was superior than placebo in relieving symptoms associated with airway obstruction. In these studies the number of side effects was little more than those of placebo, but significantly less as compared

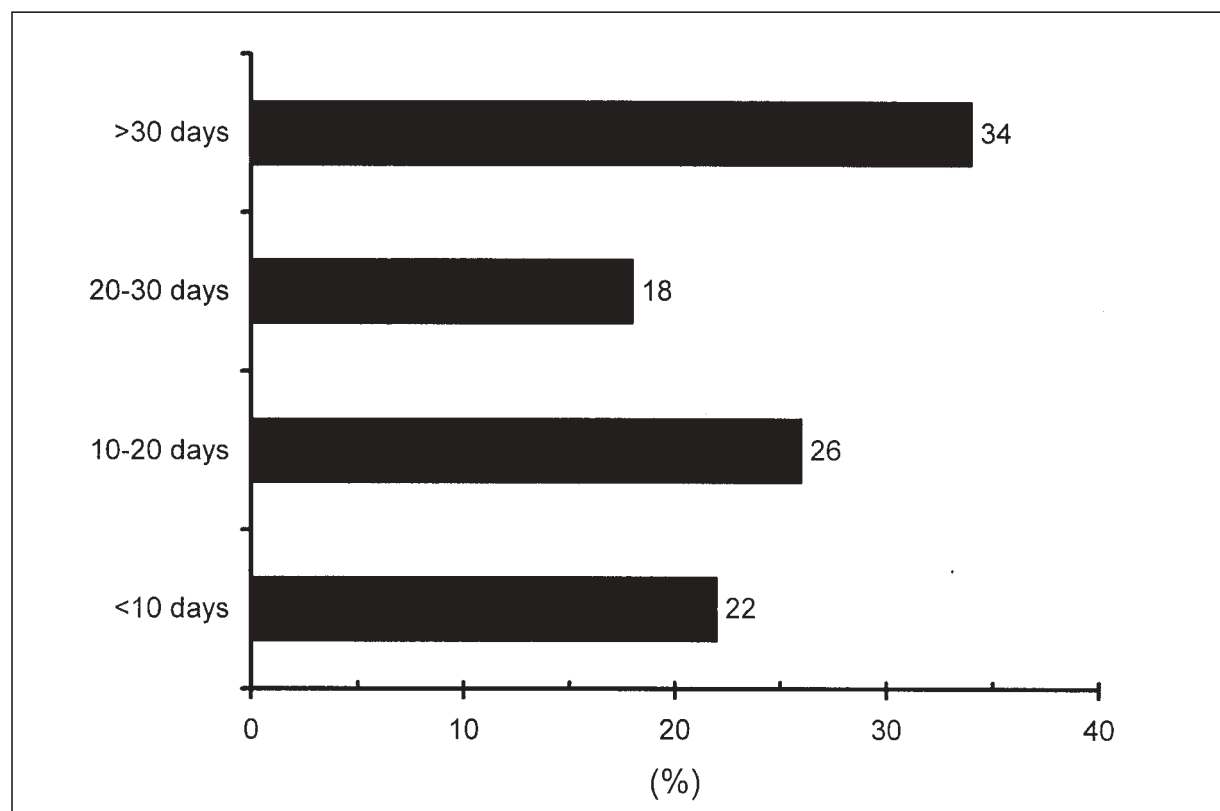


Figure 3. Duration of therapy with doxofylline in the study population.

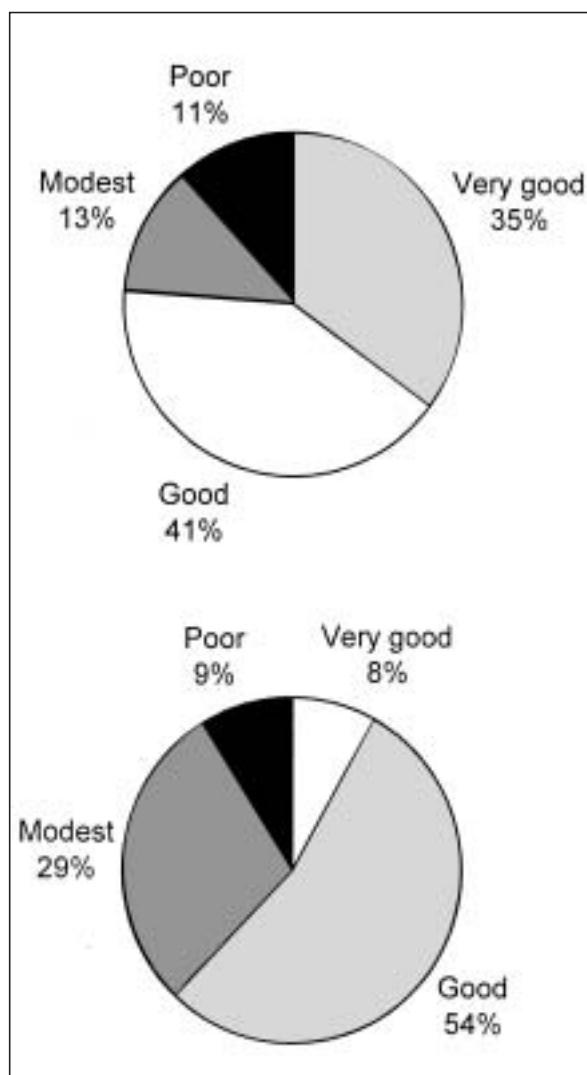


Figure 4. Overall tolerability of doxofylline (above). Overall efficacy of doxofylline (below).

to theophylline¹⁵⁻¹⁷. In the aforementioned studies a reduced frequency (compared to theophylline) of untoward effects was reported on the digestive, cardiovascular and central nervous system. As such, doxofylline was confirmed to be a safe alternative to the classical xanthine derivatives. Due to its favorable profile, most notably because of no reports of fatal events or major arrhythmias in patients treated with the drug, the therapeutic range of the compound was considered to be significantly wider with respect to that of theophylline¹⁸. Therefore, plasma monitoring is recommended only in patients with hepatic insufficiency and intolerance to xanthine drugs.

In asthmatic patients with concomitant duodenal ulcer treated with intravenous xanthines, doxofylline was not associated with a significant stimulation of gastric secretion¹⁹. The lack of any interference on cardiac rhythm with doxofylline, was demonstrated both experimentally and clinically. The 24-hour Holter monitoring performed in asthmatic patients treated with xanthine drugs, i.e. aminophylline and doxofylline, showed a less pronounced cardiostimulant effect exerted by doxofylline²⁰. Finally, in patients with chronic airway obstruction and nocturnal hypoxaemia the use of doxofylline as a respiratory medication was not accompanied by relevant alterations in their sleep architecture²¹.

In another study in 11 pediatric patients with asthma aged between 6 and 12 years, a oral daily dose of 12 mg/kg (6 mg/kg every 12 hours) of doxofylline was given for two weeks. With respect to basal values, the doxofylline treated group exhibited a significant improvement of the spirometric parameters either after 7 days or after 14 days. The differences were statistically significant compared to placebo for forced expiratory volume in one second, forced expiratory flow at mid-term of the forced vital capacity and peak expiratory flow rate. In this study neither major side effects nor drop-outs were reported²².

The data from a pediatric population of asthmatics, collected and reported in the current paper, confirmed the safety of doxofylline in a wider sample of patients. As a matter of fact, both the number of side effects definitely related to the drug and the number of drop-outs were limited, while there were no patients hospitalized because of adverse reactions associated with doxofylline. Patients treated with doxofylline were predominantly between 6 and 16 years, while only rarely the drug was given to younger patients. Concerning the dose regimen of the drug, in most of the cases doxofylline was given at a 400 mg daily dose, which corresponded mostly to 6 mg pro kg of weight every 12 hours. Non-responders treated with higher doses per kg of body weight of doxofylline (up to 9 mg pro kg of weight every 12 hours) did not exhibit any apparent relevant increase in the frequency of side effects. The mean duration of maintenance therapy was 20-to-30 days. The drug was mostly adminis-

tered in combination with bronchodilators, anti-inflammatory agents, antibiotics and mucolytics.

In conclusion, the data from this study confirmed the good tolerability of doxofylline in pediatric patients with asthma. However, since most of the patients who received doxofylline were aged more than 6 years old, further studies are required to assess the safety of the drug in younger patients.

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