ORIGINAL ARTICLE

Dipyrone Improves Small Airway Function in Asthmatic Patients With Moderate Obstruction

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Abstract

Background: Dipyrone is an analgesic and antipyretic agent with a distinctive spasmolytic effect on smooth muscles. We recently showed that dipyrone significantly relaxed precontracted tracheal smooth muscle in guinea pig.
Objective: To investigate whether this in vitro observation could be observed in vivo in the respiratory function parameters of asthma patients.
Method: Twenty-two patients, aged 18 to 75 years and diagnosed with asthma according to the American Thoracic Society criteria were enrolled at the time they had any indication for dipyrone use. Pulmonary function tests were performed before and 30, 60, 90, and 120 minutes after oral intake of 1 g of dipyrone. The tests were repeated without dipyrone intake in a situation of spontaneous recovery after a minimum washout period of 2 days.
Results: Patients were classified according to their baseline forced expiratory volume in 1 second (FEV_1) as having mild obstruction ($FEV_1 \geq 80\%$ predicted) or moderate obstruction (FEV_1 60%-80% predicted). Significant improvement with dipyrone was seen in FEV_1 and peak expiratory flow rates at 25%, 50% and 75% of forced vital capacity and in maximum midexpiratory flow rate only in patients with moderate asthma. No significant change was observed on the spontaneous recovery day except in FEV_1.
Conclusion: Dipyrone had a significant effect leading to an improved small airway function in asthmatic patients with moderate airway obstruction, confirming our recent in vitro findings.

Key Words: Asthma. Bronchodilation. Dipyrone (Metamizole sodium). Spirometry.

Resumen

Antecedentes: La dipirona es un analgésico y antitérmico con una marcada acción espasmolítica en los músculos lisos. Recientemente demostramos que la dipirona relaja significativamente el músculo liso traqueal precontraído en cobayas.
Objetivo: Investigar si esta observación in vitro podía observarse in vivo en los parámetros de función respiratoria de los pacientes asmáticos.
Métodos: Se incluyeron en el estudio 22 pacientes de entre 18 y 75 años de edad con un diagnóstico de asma según los criterios de la American Thoracic Society. En el momento de la inclusión, los participantes no requerían el uso de la dipirona. Las pruebas de función pulmonar se realizaron 30, 60, 90 y 120 minutos después de la administración de 1 g de dipirona por vía oral. Las pruebas se repitieron sin la administración de dipirona en una situación de recuperación espontánea después de un periodo de lavado de dos días.
Resultados: Los pacientes se clasificaron según los valores de referencia del volumen espiratorio forzado en el primer segundo (FEV_1) como pacientes con una obstrucción leve ($FEV_1 \geq 80\%$ del valor teórico) o con una obstrucción moderada (FEV_1 60%-80% del valor teórico). Se observó una mejora significativa con la dipirona en el FEV_1 y en los flujos espiratorios máximos en un 25%, 50% y 75% de la capacidad vital forzada y en el flujo mesoespiratorio máximo sólo en pacientes con asma moderada. No se observaron cambios significativos en el día de recuperación espontánea a excepción de en los valores FEV_1.
Conclusión: La dipirona mejora significativamente la función de las vías respiratorias pequeñas en pacientes asmáticos con obstrucción moderada de las vías respiratorias, confirmando así nuestros recientes resultados in vitro.

Palabras clave: Asma. Broncodilatación. Dipirona (metamizol sódico). Espirometría.

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Introduction

Dipyrone (metamizole sodium) is a widely-used nonopioid analgesic and antipyretic agent and is still one of the most commonly used drugs of its type in most Mediterranean countries, including Turkey, in Latin America, and in Europe [1,2]. It has been in clinical use since 1922 for mild to moderate pain, and particularly for pain associated with smooth muscle spasm, such as gastrointestinal pain, biliary, or urinary tract colic. The combination dipyrone preparations with smooth muscle relaxants once used to treat colic in the past has shifted to the use of dipyrone alone in preparations after the evaluation of spasmolytic effects of dipyrone itself in vitro and in vivo [3-5]. This smooth muscle relaxant effect has also been investigated in several systems in randomized controlled clinical trials. However, only a few studies have been done in asthmatic patients [6,7].

In a previous study, we demonstrated that dipyrone significantly relaxed precontracted tracheal smooth muscle in guinea pigs [8]. The present study was designed to investigate this effect in patients with asthma with the assumption that this context would provide a good in vivo model for studying reversible bronchodilation.

Material and Methods

This open-label study involving a single group of 22 asthma patients was carried out in accordance with the principles of the Declaration of Helsinki (2000), with the local laws and regulations relevant to the use of new and approved therapeutic agents in patients, and with the standard of the International Conference on Harmonization–Good Clinical Practice. The protocol was approved by the local ethics committee of Ankara University Faculty of Medicine (April 5, 2004; approval number, 49-1204). All patients provided written informed consent before enrollment.

Patients

Patients were eligible if they had been followed for at least 1 year after a diagnosis of asthma according to American Thoracic Society criteria: the presence of recurrent symptoms of wheezing, shortness of breath, and cough and objective signs of reversible airway obstruction (an increase in forced expiratory volume in 1 second [FEV_1] of 12% or 200 mL after inhalation of 200 μg of salbutamol) [9]. The final eligible study group consisted of patients with a minimum baseline FEV_1 value 60% of predicted and disease stability for at least 4 weeks (daily symptoms less than twice a week, nocturnal symptoms less than twice a month, no requirement for an increase in medications, no hospitalization, and no asthma attacks).

Patients were excluded if they had an acute asthma attack, hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) or dipyrone, contraindications for the use of dipyrone or any other NSAIDs (history of peptic ulcer, gastrointestinal bleeding, acute renal failure, elevated liver enzymes, and peripheral edema), history of nasal polyposis, angioedema, urticaria, or reactive bronchospasm following treatment with aspirin or other NSAIDs. Likewise, patients who were chronic drug users or abusers or in continuous treatment with prescription doses of analgesics, NSAIDs, lithium, carbamazepine, tranquilizers, or anticoagulants were also excluded. Breast-feeding women and women with demonstrated or assumed pregnancy were also excluded. The presence of a low white blood cell count or a history of blood dyscrasia was another exclusion criterion. Patients using a long-acting β_2-agonist in the last 24 hours or a short-acting β_2-agonist in the last 12 hours were excluded as well.

Study Design

The study was conducted at the allergy department of a tertiary care clinic. Eligible patients were informed about the study before their enrollment. They were told to notify us when they had pain: thus, they entered when an indication for dipyrone use developed and no asthma symptoms were present. Before the first test day, patient and disease characteristics were documented. Severity was assessed according to the guidelines of the Global Initiative for Asthma [10].

On the first test day, baseline pulmonary function was assessed and then oral dipyrone (Novalgin, Sanofi-Aventis, Istanbul, Turkey) was given at a dose of 1 g (2×500 mg) as this dose provides effective plasma levels in humans. Since a placebo arm was not possible for ethical reasons, another day was arranged to test respiratory function without dipyrone. In this sense, spirometry was repeated after a minimum washout period of 2 days without dipyrone use. All tests were started at the same time in the morning.

Spirometry was performed with a portable notebook and Medikro Spiro2000 spirometry software 1.6 version (Medikro Oy, Yrittajantie, Finland). Recorded parameters were tidal volume in liters, breathing frequency in liters per minute, vital capacity in liters, forced vital capacity (FVC, in liters), FEV_1 in liters, and the ratio FEV_1/FVC, peak expiratory flow in liters per second, maximum expiratory flow rate at 25%, 50% and 75% of FVC (MEF_{25}, MEF_{50}, and MEF_{75}, respectively, in liters per second), and maximum midexpiratory flow rate (MMEF). All parameters were measured before dipyrone intake and 30, 60, 90, and 120 minutes after dipyrone intake on the test day and on the spontaneous recovery testing day (with no pain and after washout). At least 3 technically correct determinations with no more than 5% variation were recorded and the best was accepted. All parameters were also expressed as percentages of predicted using the prediction equation of Kory [11].

Efficacy and Safety Assessments

The effect of dipyrone on respiratory function in asthma patients was evaluated by comparing the spirometric

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parameters before and after drug intake. The primary endpoint was change in FEV_1. Secondary endpoints were changes in other obstructive parameters including MEF_{25}, MEF_{50}, MEF_{75}, and MMEF.

Since there are many reports of analgesic intolerance and the bronchospastic effect of dipyrone on asthma patients [12], safety was carefully evaluated by recording spontaneously reported adverse events and by asking about adverse reactions throughout the study period.

Statistical Analysis

All lung function results were expressed as mean ± SEM for the test parameters. Patient characteristics were expressed as mean ± SD. Comparisons of the corresponding levels at the determined time intervals and analysis to detect a carry-over effect on baseline spirometric values on 2 nonconsecutive treatment days were performed by Friedman variance analysis. A Wilcoxon test was used in cases for which statistically significant differences in spirometric parameters were detected in the Friedman analysis. Changes from baseline in lung function parameters after intake of dipyrone were given as absolute values and as percentage increases. Significance was set at a *P* value lower than .05. The Statistical Package for Social Sciences version 11.0 for Windows (Chicago, Illinois, USA) was used to analyze the data.

Results

Initially 22 patients (19 females) aged between 31 and 64 years were recruited. Two patients who had baseline FEV_1 values of less than 60% of predicted were excluded. Finally, 20 subjects were considered eligible for study. Figure 1 is a flow chart for the study.

Twenty percent of patients were smokers, with an average smoking history of 7 pack-years. Patient, disease, and treatment characteristics are summarized in the table.

Measures of Effect and Safety

Baseline spirometry on the nonconsecutive study days (dipyrone test day and the recovery day) indicated that lung function variables were comparable. Thus, the baseline spirometric data of 2 days were averaged for the remaining analyses.

No significant change was observed in mild asthma patients in any of the test parameters at any time point (Figure 2). In moderate asthma patients, however, after 1 g of oral dipyrone intake, the mean increase in FEV_1 of 0.06 L (5%) at 30 minutes was significantly higher than at baseline (Figure 3). These results are consistent with the pharmacokinetic profile of dipyrone [13].

The mean improvement in maximum increase in FEV_1 over baseline values was 0.11 L (8%) and occurred 90 minutes after dipyrone intake in moderate asthmatics (Figure 3). These results are also consistent with the pharmacokinetic profile of dipyrone [13]. FEV_1 improved significantly over baseline values for 120 minutes after dipyrone intake. The mean increase in FEV_1 over baseline 120 minutes after dipyrone intake was 0.10 L (8%) in moderate asthma patients (Figure 3).

As we did not observe any significant change in the spirometry of normal healthy volunteers in a previous study [14], baseline values of asthma patients were compared with those control subjects' values; no significant differences were found.

Modest but significant improvement was seen in MEF_{25}, MEF_{50}, MEF_{75}, and MMEF values 30, 60, 90, and 120 minutes after dipyrone intake in patients with moderate obstruction (Figure 3). The improvement in MMEF 90 minutes after dipyrone intake was 26%. Furthermore, a clear time-trend improvement in small airway parameters was observed, apparently consistent with in vitro results [8].

On the spontaneous recovery day, the improvement in FEV_1 was comparable to the improvement obtained after dipyrone use. No significant change in other lung function parameters was observed.

Patient, Disease, and Treatment Characteristics*

	Whole Group	Mild Asthma Patients	Moderate Asthma Patients
Number	20	9	11
Age, y, mean ± SD	45 ± 8	41 ± 7	50 ± 8
Gender	17F, 3M	9F	8F, 3M
Disease duration, y, mean ± SD	10 ± 8	6 ± 5	16 ± 8
Atopy, n (%)	11 (79%)	7 (78%)	4 (80%)
Initial FEV_1, % of predicted	≥60%	≥80%	≥60% and <80%
Medications, n (%)			
I. Inhaled steroids			
– 500 µg BDP or equivalent†	9 (45%)	6 (67%)	3 (33%)
– 500-1000 µg BDP or equivalent†	11 (55%)	7 (64%)	4 (36%)
II. Antileukotrienes	2 (10%)	1 (5%)	1 (5%)

*F indicates female; M, male.

†250 µg fluticasone = 500 µg beclomethasone (BDP) = 400 µg budesonide

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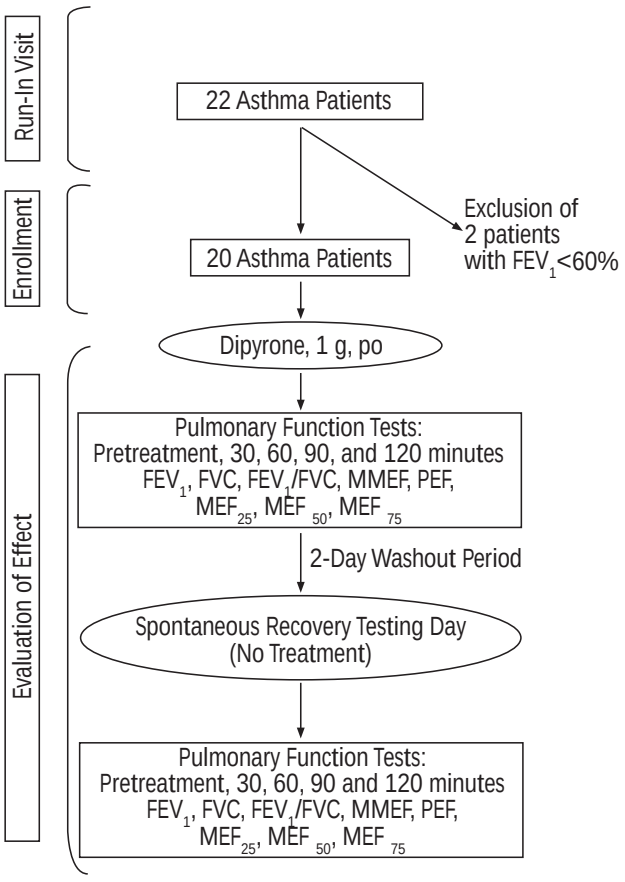

Figure 1. Flow chart of steps in the study. FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximum midexpiratory flow rate; PEF, peak expiratory flow rate; MEF_{25}, MEF_{50}, MEF_{75}, maximum expiratory flow rate at 25%, 50% and 75% of FVC; po, per oral.

All patients completed the study without any adverse event (Figure 1). Moreover, none of them needed additional bronchodilator therapy in the 12 hours of follow-up.

Discussion

As our previous in vitro model showed a spasmolytic effect of dipyrone on precontracted smooth muscle and no or minimum effect on basal muscle tonus [8], we thought that asthma, with its reversible airway obstruction, could provide a good clinical model for demonstrating a spasmolytic (bronchodilatory) effect of dipyrone in vivo.

In this study, we demonstrated that dipyrone affected small airways, leading to an improvement in MEF_{25}, MEF_{50}, MEF_{75} and MMEF values only in patients with lower baseline FEV_1 values. Although a significant increase in FEV_1 values were also observed in the same group, this effect cannot be regarded as significant bronchodilation caused by dipyrone in our trial because the results of testing on the spontaneous recovery day showed similar enhancement for FEV_1. Our observation of no effect on large airway smooth muscle (by means of no improvement in FEV_1) was a quite interesting finding, as our in vitro study had revealed a spasmolytic effect on larger airways [8]. However, it might still be possible to see the effect of dipyrone on FEV_1 with a larger number of participants. The improvement in spirometry findings in asthmatics with lower baseline FEV_1 values started 30 minutes after intake of dipyrone and the peak value was observed at 60 minutes, consistent with the pharmacokinetic profile of dipyrone [13].

The respiratory tract smooth muscle relaxing effect of dipyrone has been reported in a small number of clinical trials. In a case reported by Hady [6], it was reported that premedication with dipyrone allowed the bronchoscope to pass through the bronchus more easily and increased the gas exchange in the lungs. Dipyrone was also found to increase the gas exchange in the lungs when given as an analgesic for postoperative pain relief. In the light of these findings, dipyrone was given to 82 patients suffering from an asthma attack. In all of the patients, the intravenous injection of dipyrone interrupted the attack, leading to immediate disappearance of cyanosis and the relief of chest tightness. Resta et al [7] also reported on 2 asthma patients whose airway obstructions improved with dipyrone.

Another point to be highlighted is the claim that the spasmolytic effect of dipyrone affects precontracted smooth muscle, in other words it has no effect or a minimum effect on basal muscle tonus. This claim has been demonstrated in the current study, in which the bronchodilatory effect of dipyrone was only seen in patients with FEV_1 values between 60% and 80% and could not be observed in patients with baseline FEV_1 values 80% of predicted or more. Similarly, our previous study also documented no improvement in spirometric tests in normal healthy subjects with no baseline airway obstruction [14]. However, severe asthma patients with baseline FEV_1 values less than 60% of predicted were not included in the study, for ethical reasons. Further trials evaluating whether the smooth muscle relaxing effect of dipyrone is greater in patients with more prominent airway obstruction or in the presence of another bronchodilator agent could be of interest.

However, precontracted status of the airways is not the only factor that seems to determine the response to dipyrone. Underlying airway reversibility seems to be relevant as well. In this trial, all patients had an airway reversibility of at least 12% percent in FEV_1 and we observed a significant effect on certain parameters. Our recent study performed on patients with COPD with poor airway reversibility, on the other hand, revealed no significant improvement in spirometry in this group of patients, suggesting the relevance of underlying airway reversibility on response to dipyrone [14].

The mechanism by which dipyrone relieves bronchospasm is not clearly understood. Although anti-inflammatory properties by way of cyclooxygenase (COX) enzyme and thus prostaglandin synthesis inhibition by NSAIDs is thought to be responsible for the spasmolytic effect of some NSAIDs, as dipyrone has no or minimal anti-inflammatory effect, COX inhibition can not be the definite explanation for dipyrone's spasmolytic effect. In an early study, Szczeklik and Nizankowska [15] reported 6 asthma cases in which

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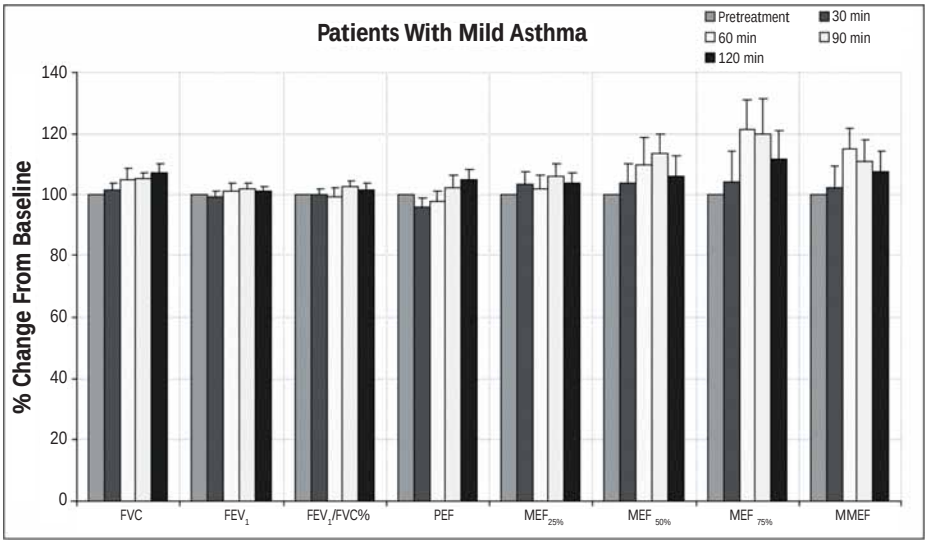

Figure 2. Main spirometry findings for the 9 patients with mild asthma (baseline forced expiratory volume in 1 second [FEV_1], ≥80%). Data are shown as percentage of change from baseline after dipyrone intake. The whiskers indicate the SEM. FVC indicates forced vital capacity; MMEF, maximum midexpiratory flow rate; PEF, peak expiratory flow rate; MEF_{25}, MEF_{50}, MEF_{75}, maximum expiratory flow rates at 25%, 50% and 75% of FVC.

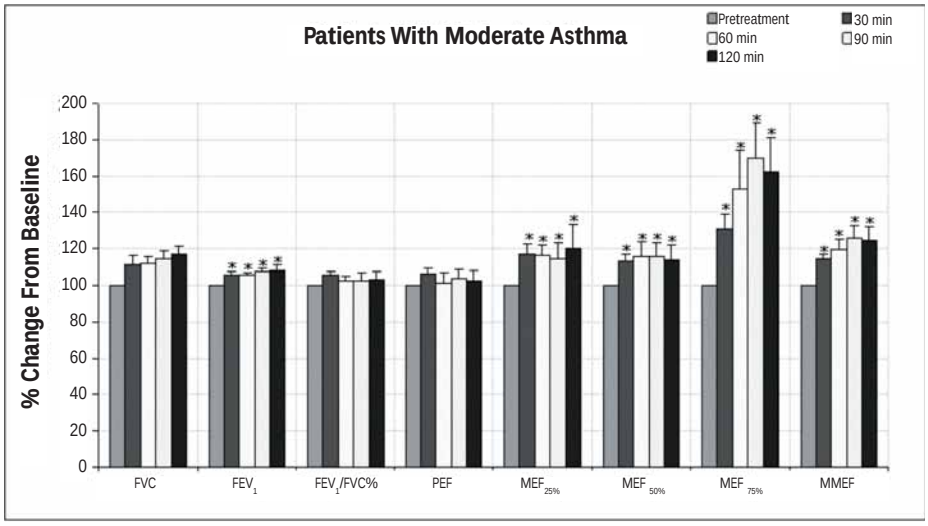

Figure 3. Main spirometry findings for the 11 patients with moderate asthma (baseline forced expiratory volume in 1 second [FEV_1], 60%-80% of predicted). Data are shown as percentage of change from baseline after dipyrone intake. The whiskers indicate the SEM. FVC indicates forced vital capacity; MMEF, maximum midexpiratory flow rate; PEF, peak expiratory flow rate; MEF_{25}, MEF_{50}, MEF_{75}, maximum expiratory flow rate at 25%, 50% and 75% of FVC.

there was significant improvement in pulmonary function tests and clinical parameters with aspirin use. Two patients also showed improvement with other NSAIDs, suggesting that COX-1 enzyme inhibition could have been responsible. Although classified as an NSAID, dipyrone is a weak inhibitor of COX-1 and COX-2, or probably an inhibitor of the COX enzyme variant, COX-3 [16]. Moreover, the smooth muscle relaxing effect of dipyrone has been reported in many randomized, controlled clinical trials on the common bile duct [17], Oddi sphincter tonus [18], efferent urinary tract and urinary vesicle [19] as well as the respiratory tract [6,7], suggesting that dipyrone has a unique action on smooth muscles regardless of COX enzyme inhibition. In addition to this, in our recent study, we demonstrated a dipyrone-mediated decrease in ATP-induced intracellular free calcium levels and the inhibition of G protein-coupled receptor-stimulated inositol phosphate (IP) accumulation [8], suggesting that the mechanism of the spasmolytic effect may be due to inhibiting the IP-mediated release of calcium from intracellular stores. The point to be emphasized here is the occurrence of a spasmolytic effect of dipyrone on precontracted smooth muscle, rather than on basal muscle tonus. However, the mechanism needs to be clarified in detail by further studies.

It would also be of interest to see the similar improvement in lung function parameters with other NSAIDs. However, this study mainly focused on the spasmolytic effect of dipyrone on bronchial smooth muscles based on our previous in vitro study [8]; therefore we did not perform oral challenge tests with other NSAIDs. Regarding the existence of some asthma patients who benefit from aspirin and aspirin-like drugs, evident in lung function test findings and clinically, it could also be interesting whether this improvement can be observed with various NSAIDs.

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On the other hand, one should bear in mind that analgesic intolerance is a common problem in asthma patients and some asthma patients describe increased dyspnea after use of aspirin and related COX-1 inhibitors. Although the main mechanism of hypersensitivity reactions of NSAIDs is the inhibition of COX-1 resulting in a decrease in protective prostaglandin E2 followed by an increase in cysteinyl leukotrienes, immunoglobulin-E–mediated reactions involving specific antibodies to pyrazolone derivatives seem to be the major mechanism of hypersensitivity reactions to dipyrone [20-24]. Thus, there may be patients demonstrating an adverse reaction to dipyrone alone as well as cross reacting with other NSAIDs. Physicians mostly do not prefer dipyrone as an analgesic and antipyretic agent for asthma patients. During our study, patients had no history of sensitivity to NSAIDs or dipyrone and no adverse events occurred. Therefore, physicians must be careful to ask about hypersensitivity reactions to NSAIDs as well as to other drugs before recommending dipyrone to asthma patients.

One limitation of this study is the lack of a placebo arm for ethical reasons. However, we had another control day without dipyrone use (the spontaneous recovery testing day) for the assessment of the usual effect of the circadian rhythm on pulmonary function parameters. Accordingly, an improvement in FEV_1 both after dipyrone use and on the control day suggested that this improvement was spontaneous and not unique to dipyrone use. However, improvement in parameters reflecting the small airways on the dipyrone test day but lack of improvement in such parameters on the control day suggested that these effects are related to dipyrone use. This study was mainly designated for investigating in vivo effect of dipyrone, as such an effect had been previously shown in vitro [8], and we did not explore the clinical use of dipyrone in asthma as a bronchodilator. Therefore, despite the lack of placebo arm, we believe that the dipyrone-free control day provided strong evidence of an effect of dipyrone on certain pulmonary function test parameters.

In conclusion, this study showed that dipyrone has a spirometrically and eventually clinically evident smooth muscle relaxing effect especially on small airways, supporting in vitro results about the occurrence of a spasmolytic effect of dipyrone on precontracted smooth muscle. Whether dipyrone potentiates the effect of standard bronchodilatory agents may be another research subject as it has not been evaluated yet.

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