Respiratory Medicine (2006) **100**, 828–834

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Does dipyrone have any effect on respiratory function in COPD patients? ☆

S. Ezgi Gulmez[a,*], F. Cankat Tulunay[a], Sumru Beder[b], Oya Kayacan[b], Demet Karnak[b]

[a]*Department of Pharmacology and Clinical Pharmacology, Medical School of Ankara University, 06100 Sihhiye, Ankara, Turkey*
[b]*Department of Chest Diseases, Medical School of Ankara University, 06100 Ankara, Turkey*

Received 22 April 2005; accepted 6 September 2005

KEYWORDS
Dipyrone (metamizole);
Chronic obstructive pulmonary disease (COPD);
Bronchodilation;
Spirometry

Summary
Objective: Dipyrone (Novalgin®) is an effective analgesic, antipyretic agent also with spasmolytic effects on various types of smooth muscles. It has recently been reported that dipyrone relaxes tracheal smooth muscle of guinea pig. In this present study, we aimed to investigate whether this and previously reported in vitro results have any consequences on the respiratory function of normal healthy volunteers and chronic obstructive pulmonary disease (COPD) patients.
Methods: In this one-centered, non-randomized, non-comparative, open labelled study, 15 normal healthy volunteers and 15 stable COPD patients, with partially reversible bronchospasm, diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were enrolled in the study at the time they had any indication of dipyrone use. The spirometric tests were performed by a portable notebook and Medikro Spiro2000 spirometry programme-software 1.6 version, before 30, 60, 90, and 120 min after 20 mg/kg of orally dipyrone intake. Groups were compared with the General Linear Model Repeated Measures analysis of variance.
Results: None of the spirometric parameters evaluated showed any significant differences when compared with the baseline values in both groups.
Conclusion: While dipyrone had no bronchodilator effects on either COPD patients or normal volunteers, it also did not impair the spirometric parameters. Since COPD is a disease characterized by a progressive and largely irreversible airflow limitation, dipyrone has no observable bronchodilator effect. However, since dipyrone does not

☆This study has been presented at the 14th Annual Congress of The European Respiratory Society, September 4–8, 2004, Glasgow, Scotland.

*Corresponding author. Tel.: +90 312 3095293; fax: +90 312 3116495.
E-mail addresses: gulmez@medicine.ankara.edu.tr, gulmezezgi@yahoo.com (S.E. Gulmez).

0954-6111/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2005.09.002

impair the pulmonary function, it can be used safely in COPD patients when there is an indication.
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Introduction

Dipyrone is a non-opioid analgesic and antipyretic agent that has been in clinical use since 1922. It is used for moderate to severe pain as well as pain due to smooth muscle spasm or colic pain. The combination preparations of dipyrone with smooth muscle relaxing agents, used to treat colic pain in the past years, were changed to single dipyrone preparations after the evaluation of the self-spasmolytic effects of dipyrone.

The spasmolytic effect of dipyrone has been shown in many in vitro and in vivo experimental studies. For instance, dipyrone dose dependently inhibits barium-chloride-induced isolated rat ileum as well as electrically stimulated, isolated guinea pig ileum contractions.[1] It has also been shown that dipyrone antagonizes histamine, serotonin and bradykinin-induced bronchospasm in guinea pigs.[2,3] Despite the well-known spasmolytic effect of dipyrone and the presence of many in vitro, in vivo studies and clinical trials showing this effect, its mechanism of action needs to be clarified. In a previous study, we demonstrated that dipyrone significantly relaxed *pre-contracted* tracheal smooth muscle in guinea pigs.[4]

There are many randomized, controlled clinical studies investigating this smooth muscle relaxing effect on different systems. It has also been shown that dipyrone reduces the common bile duct and Oddi sphincter tonus in a dose-dependent manner as well as efferent urinary tract and urinary vesicle motility.[5–9]

The smooth muscle relaxing effect of dipyrone on the respiratory tract was also shown in clinical trials, in asthmatic patients. In 1973, Hady reported that premedication with dipyrone eased the bronchoscopic procedure. Also, dipyrone was 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 resulting in immediate disappearance of cyanosis and the relief of chest tightness.[10] Resta et al.[11] reported two typical asthmatic cases whose airway obstruction improved by dipyrone and other non-steroidal anti-inflammatory drugs (NSAIDs). The patients' forced expiratory volume in the first second (FEV_1) values increased in 15–30 min and bronchodilation was confirmed by spirometric tests. When dipyrone was given to the patients, FEV_1 values increased up to a peak of 150% of their baseline values at 60 min and the bronchodilatory effect lasted for 5 h.

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world.[12] It is estimated that COPD will be the third cause of mortality in 2020.[13] The revised Global Initiative for Chronic Obstructive Lung Disease (GOLD) describes COPD as a disease state characterized by progressive airflow limitation that is not fully reversible conversely to asthma and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[14] The two important points about this definition is that inflammation is the main mechanism underlying airway abnormalities in COPD patients, and that smoking is not the only etiological factor although COPD is mostly seen in smokers.[15]

Despite its bronchodilatory effect on asthmatic patients, dipyrone has not been studied in COPD patients. This present study was performed to investigate whether the in vitro smooth muscle relaxing-bronchodilatory effects of dipyrone have any consequences on partially reversible COPD patients, as we had known that dipyrone can affect the *pre-contracted* smooth muscle. We investigated whether COPD patients would benefit from this smooth muscle relaxing effect when dipyrone was chosen as the analgesic agent. We also evaluated its effect on normal healthy volunteers.

Material and methods

This one-centered, non-randomized, non-comparative, open-labelled study involving 15 normal healthy volunteers and 15 COPD patients was performed in accordance with the Declaration of Helsinki, with the local laws and regulations relevant to the use of new and approved therapeutic agents in patients and the International Conference on Harmonization-Good Clinical Practice standard. COPD patients were diagnosed according to the GOLD criteria. The protocol was approved by the local ethics committee of the Medical School of Ankara University (October 20, 2003; approval number: 39-990). All volunteers and

patients provided written informed consent before their enrolment in the study.

Subjects and inclusion criteria

Fifteen normal healthy volunteers (seven male, eight female) were enrolled in the study, as well as 15 (13 male, two female) stable and partially reversible COPD subjects diagnosed according to GOLD criteria at the time they had any indication of dipyrone use. The COPD patients were between 44 and 78 years old, with no history of any adverse events related to dipyrone. Since we aimed to investigate whether we could show the smooth muscle relaxing effects of dipyrone in normal healthy volunteers or in COPD patients, a randomization schema for the study was not prepared. Only, partially reversible COPD patients who would receive dipyrone for any indication were enrolled into the study, to be observed for 2 h.

Exclusion criteria

Patients with acute exacerbation of COPD and patients with bronchiectasis, pure emphysema with no airflow limitation and asthma were not included in the study. Also, patients were excluded if they had hypersensitivity to NSAIDs or dipyrone, contraindications for the use of dipyrone or any other NSAIDs (history of peptic ulcer, gastrointestinal bleeding, elevated liver enzymes, peripheral oedema and acute renal failure), history of nasal polyposis, angioedema, urticaria, or reactive bronchospasm following treatment with aspirin or other NSAIDs. Patients with chronic drug use or drug abuse or in continuous treatment with prescription doses of analgesics, NSAIDs, lithium, carbamazepin, tranquilizers and anticoagulants were also excluded. Breast-feeding women and women with proven or assumed pregnancy were not included.

Study design

The spirometric tests were performed by a portable notebook and the Medikro Spiro 2000 spirometry programme-software 1.6 version. The main spirometric parameters of tidal volume (TV, l), frequency rate (FR, l/min), mean volume (MV, l/min), vital capacity (VC, l), forced vital capacity (FVC, l), FEV_1 (l), FEV%, peak expiratory volume (PEF, l/s), maximum expiratory flow rate 25% (MEF_{25}, l/s), maximum expiratory flow rate 50% (MEF_{50}, l/s), maximum expiratory flow rate 75% (MEF_{75}, l/s), maximum mid-expiratory flow rate (MMEF), forced inspiratory vital capacity (FIVC, l), forced inspiratory volume in first second (FIV_1, l), forced inspiratory volume % (FIV%), peak inspiratory volume (PIF, l/s), maximum voluntary volume (MVV, l/min), maximum voluntary volume frequency rate (MVVFR, 1/min), maximum voluntary volume time (MVVT, s) were measured before, 30, 60, 90 and 120 min after dipyrone intake. Dipyrone was given as an oral suspension at a dose of 20 mg/kg. COPD patients were enrolled in the study at the time they had any indication for dipyrone use and they were allowed to get their regular treatment.

Efficacy assessment

The effect of dipyrone on respiratory function in normal healthy volunteers and in COPD patients was evaluated by comparing the spirometric parameters before and after drug intake. A 12% increase compared with baseline FEV_1 values was considered as the bronchodilator effect of dipyrone.

Safety assessment

Safety was assessed by monitoring the adverse events throughout the study period.

Statistical methods

For both groups, the effect of dipyrone was evaluated with the General Linear Model Repeated Measures analysis of variance by using SPSS 9.0 for Windows.

Results

All of the normal healthy volunteers completed the study without any adverse events. An adverse event characterized by bronchospasm occurred in one of the COPD patients and the data obtained from this patient were excluded from further analysis (Fig. 1).

Demographic data

Seven male (46.6%) and eight female normal healthy volunteers (age range: 23–59 years), and 13 male (86.6%) and two female COPD patients (age rage: 44–78 years), were enrolled in the study. Demographic data of the subjects are tabulated in Table 1. The mean COPD duration was 8 years. Sixty-seven percent of the patients with COPD were smokers with an average of 39 pack-year smoking history.

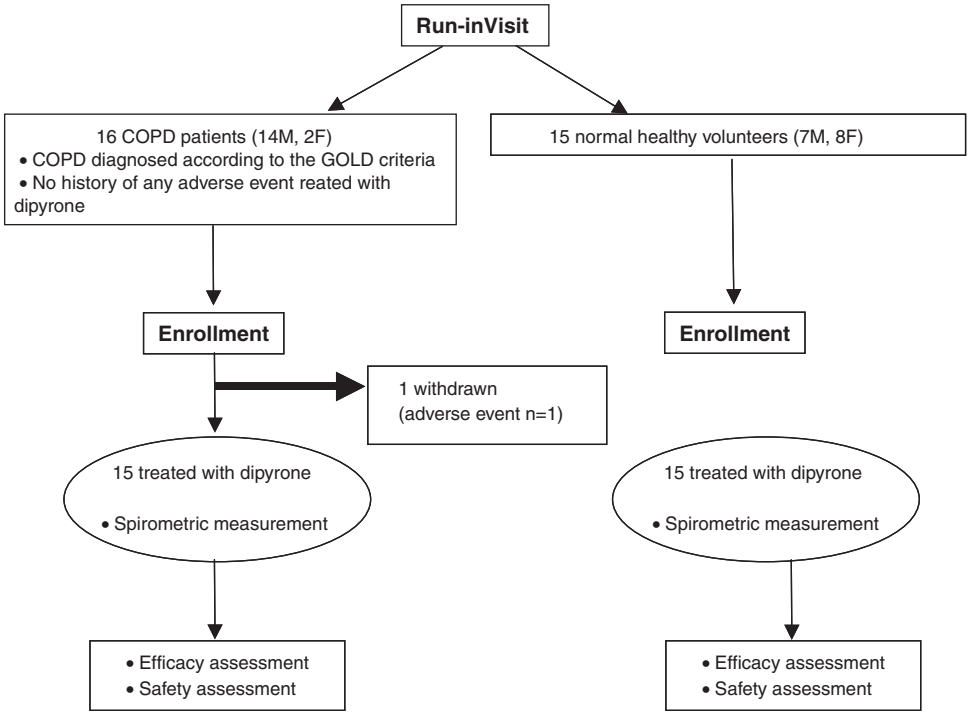


Figure 1 Study outline is figured out briefly.

Table 1 Demographic data of the enrolled subjects.

Group	*N*	Gender	Age (years ± SD)	Height (cm ± SD)	Smokers (%)
Normal healthy volunteers	15	7M, 8F	32 ± 3	165 ± 5.2	26.6
COPD patients	15	13M, 2F	64 ± 2	170 ± 4.3	67

Spirometric parameters

We did not observe any significant change in the spirometric parameters in either normal healthy volunteers or COPD patients (Figs. 2 and 3, respectively).

Adverse events

All of the normal healthy volunteers and COPD patients except one in the COPD group completed the study without any adverse events during the study. An adverse event, characterized by dyspnea, wheezing and cough occurred in one COPD patient 45 min after dipyrone intake. The patient recovered totally after treatment with bronchodilators. The patient was excluded from the study. The relation between drug exposure and the bronchospasm was estimated as "possible" when evaluated by the Naranjo Adverse Drug Reaction (ADR) scale.[23]

Discussion

Spirometric tests are useful in determining the airflow limitation degree, in evaluating the response to treatment and pursuing the clinical prognosis.[16] Together with the presence of symptoms, spirometry helps to stage COPD severity and can be a guide to specific treatment steps. FEV_1 and FEV_1/FVC ratio are the most valuable parameters in evaluating the obstructive pattern. The decrease in these parameters is considered as obstruction in large airways; the lower the percentage predicted FEV_1, the worse the subsequent prognosis. MEF_{25}, MEF_{25-75}, MEF_{75} and MMEF are the valuable spirometric parameters to evaluate small airways. A normal value for spirometry effectively excludes the diagnosis of clinically relevant COPD. In COPD patients, FVC, FEV_1 values and FEV_1/FVC ratios are typically lower than normal values. Normally, 75–80% of the inspired air should be expired during the first second of expiration. COPD patients have less than 80% FEV_1

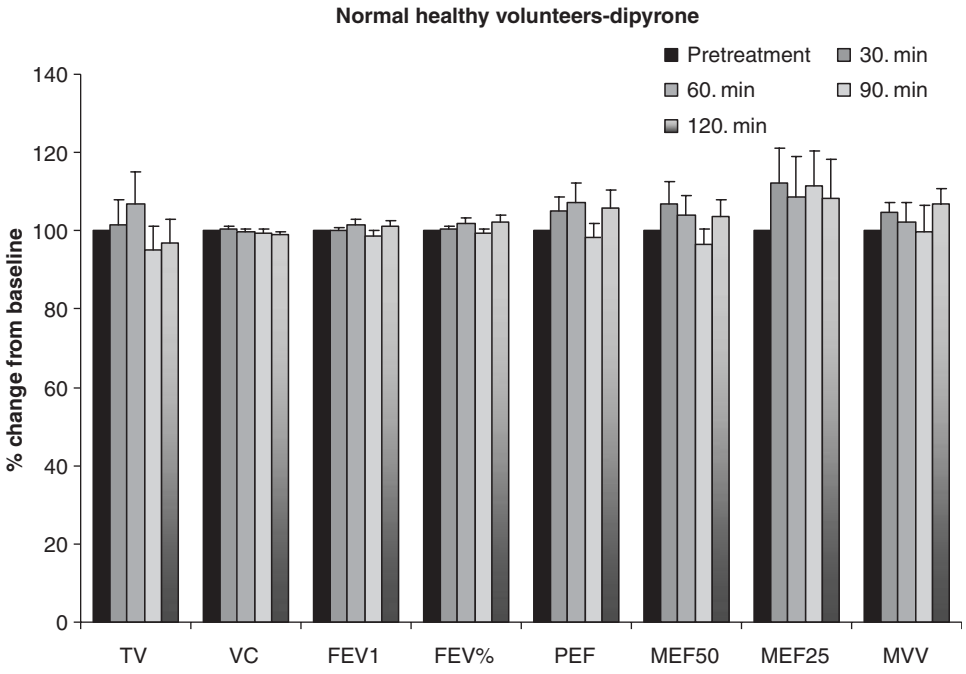


Figure 2 Main spirometric parameters of normal healthy volunteers. Data are shown as percentage change from baseline after dipyrone intake+standard error of mean (SEM).

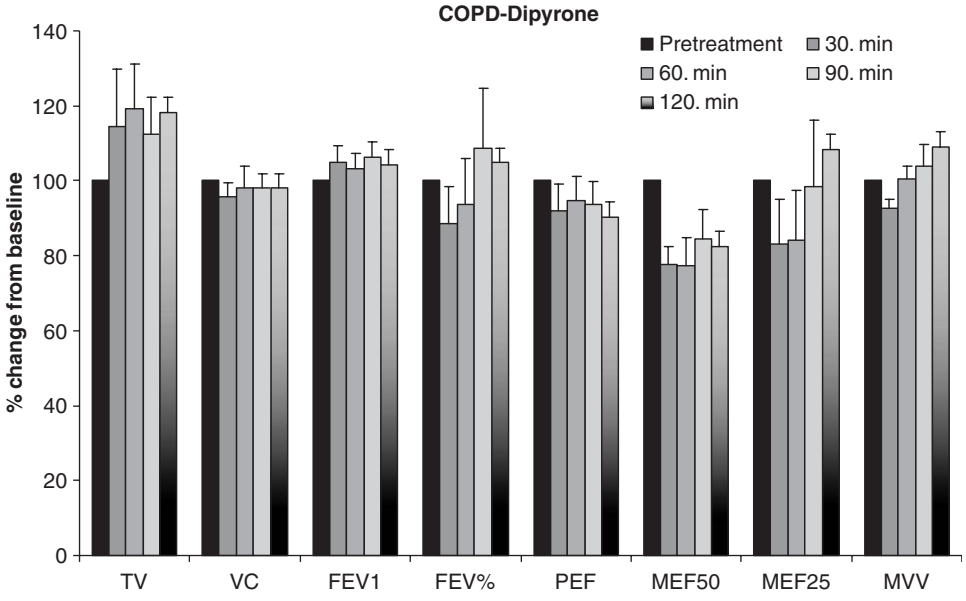


Figure 3 Main spirometric parameters of COPD patients. Data are shown as percentage change from baseline after dipyrone intake+standard error of mean (SEM).

values, and less than 70% FEV_1/FVC ratios of the predicted values.

In controversy to asthma, COPD is an irreversible or partially reversible obstructive disease. Most patients' FEV_1 values only increase less than 15% of the baseline value after one puff of short-acting β_2 agonist. The patients showing 15–20% increase in FEV_1 comprise the "partially reversible" subjects. In spite of this increase, FEV_1 values of COPD patients never reach the normal predicted values.[17] Another important point is that, even though the patients do not show significant FEV_1 response to short-acting bronchodilator agonists, they may benefit symptomatically from long-acting bronchodilator treatment. Most of the COPD patients who are given a sufficiently strong

bronchodilator medication will exhibit at least a 10% increase in maximal expiratory airflow and a reduction in hyperinflation and dyspnea, and an increase in the exercise capacity.[18–20]

Drugs, which increase FEV_1 values or change other spirometric values by acting on the airway smooth muscles, are termed as ''bronchodilator agents''. They are approved as the main group of agents for the symptomatic treatment of COPD. The spasmolytic effect of dipyrone on various organs such as vessels, urether, and bile duct is a well-known effect. In a previous study, we demonstrated that dipyrone significantly relaxed *precontracted* tracheal smooth muscle in guinea pigs.[4] To the best of our knowledge, no randomized clinical trial evaluating the bronchodilatory effect of dipyrone in COPD patients has been done. In this unique study on COPD patients, the effect of dipyrone on spirometric parameters was examined, foreseeing that the patients may benefit from its spasmolytic effect when chosen as an analgesic alternative. Neither normal healthy volunteers nor COPD patients showed statistically significant change on spirometric parameters 30, 60, 90 and 120 min after drug intake. According to these results, we conclude that the smooth muscle relaxing effect of dipyrone could not be seen in COPD patients although these patients were partially reversible. The result is not surprising for normal healthy volunteers since dipyrone has no effect on basal smooth muscle tonus.

NSAID-induced bronchospasm is a common and serious problem. A report from MEDSAFE, the New Zealand Medicines and Medical Devices Safety Authority, informs that between 8% and 20% of adult asthmatics experience bronchospasm following ingestion of aspirin and other NSAIDs.[21] The administration of NSAIDs to patients with asthma might result in three different responses—bronchoconstriction, bronchodilatation or lack of bronchopulmonary action. Also, there are some case reports about NSAID-induced bronchospasm.[22] In the present study, bronchospasm possibly induced by dipyrone was observed in one COPD patient who responded well to the bronchodilators. The adverse event was diagnosed by clinical symptoms and spirometric tests. The relationship between drug exposure and the bronchospasm was estimated as ''possible'' when evaluated by the Naranjo ADR scale.[23] Using this scale, the causality estimation did not totally prove that bronchospasm was induced by dipyrone. Normal healthy volunteers and other COPD patients did not exhibit any worsening in spirometric parameters showing that dipyrone is a safe agent in COPD patients.

Conclusion

No bronchodilator effect of dipyrone in COPD patients was observed. On the other hand, we believe that it can be safely used in such patients when indicated.

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