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

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respiratoryMEDICINE

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

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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.

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0954-6111/$ - see front matter
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.

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