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RESEARCH PAPER

Co-administration of pentoxifylline and thiopental causes death by acute pulmonary oedema in rats

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Background and purpose: Pentoxifylline exhibits rheological properties that improve microvascular flow and it is widely used in vascular perfusion disorders. It also exhibits marked anti-inflammatory properties by inhibiting tumour necrosis factor α production. Thiopental is one of the most widely used drugs for rapid induction of anaesthesia. During experimental studies on the treatment of acute pancreatitis, we observed that when pentoxifylline was administered after anaesthesia with thiopental, most of the rats exhibited dyspnea, signs of pulmonary oedema and died. The aim of the work described here was to investigate the cause of the unexpected toxic effect of the combined treatment with thiopental and pentoxifylline.
Experimental approach: Pulmonary vascular permeability and arterial blood gases were measured, and a histological analysis was performed. The possible role of haemodynamic changes in the formation of pulmonary oedema was also assessed.
Key results: Co-administration of pentoxifylline and thiopental increased pulmonary vascular permeability and markedly decreased arterial pO_2, with one third of rats suffering from hypoxemia. This combined treatment caused death by acute pulmonary oedema in 27% of normal rats and aggravated the respiratory insufficiency associated with acute pancreatitis in which the mortality rate increased to 60%. This pulmonary oedema was not mediated by cardiac failure or by pulmonary hypertension.
Conclusions and Implications: Co-administration of pharmacological doses of pentoxifylline and thiopental caused pulmonary oedema and death in rats. Consequently, pentoxifylline should not be administered when anaesthesia is induced with thiopental to avoid any possible risk of acute pulmonary oedema and death in humans.
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Keywords: lung oedema; vascular permeability; hypoxemia; thiopental; pentoxifylline; drug interaction

Abbreviations: ABF, aortic blood flow; BSA, body surface area; FITC, fluorescein isothiocyanate; MPAP, mean pulmonary artery pressure; NO, nitric oxide; RVEP, right ventricular end-diastolic pressure; VEGF, vascular endothelial growth factor

Introduction

Pentoxifylline is a drug widely used in clinical practice to treat disorders of vascular perfusion, particularly cerebrovascular diseases and diseases of the peripheral circulation such as intermittent claudication (Ward and Clissold, 1987). This methylxanthine derivative exhibits rheological properties that improve microvascular flow by increasing blood cell deformability, decreasing platelet aggregation, lowering blood viscosity, reducing thrombus formation and acting as a peripheral vasodilator (Ward and Clissold, 1987). More recently, pentoxifylline has also been used as an anti-inflammatory agent in chronic diseases, such as sarcoidosis (Baughman *et al.*, 2003). It exhibits marked anti-inflammatory properties mediated mainly by inhibition of tumour necrosis factor α production (Schandené *et al.*, 1992). We have found that pentoxifylline reduces pancreatic interstitial oedema and infiltration of inflammatory cells into the pancreatic and pulmonary tissues in experimental acute pancreatitis (Gómez-Cambronero *et al.*, 2000; Pereda *et al.*, 2004). According to these results, pentoxifylline may also be considered as potential therapy in acute pancreatitis. At present there are clinical trials going on to assess the therapeutic efficacy of pentoxifylline in the treatment of this disease.

While performing our experimental studies on the treatment of acute pancreatitis, we observed that most of the rats

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with pancreatitis died when pentoxifylline was given following anaesthesia with thiopental. It is noteworthy that, at present, thiopental is one of the most widely used drugs for rapid induction of anaesthesia in Western countries (Morris and Cook, 2001). The aim of the work described here was to investigate the cause(s) of the unexpected lethal effect of the co-treatment with thiopental and pentoxifylline. In preliminary experiments, the rats with acute pancreatitis subjected to this co-treatment exhibited dyspnea and necropsy revealed signs of pulmonary oedema. Consequently, our hypothesis was that death following the combination of thiopental and pentoxifylline was caused by pulmonary oedema and respiratory insufficiency.

Methods

Animals and dosage

Male Wistar rats (250–350 g) were used. All animal experiments conformed to the revised Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council '*Guide for the Care and Use of Laboratory Animals*' National Academy Press, Washington, DC, 1996. The Research Committee of the School of Medicine (University of Valencia, Spain) approved the study protocol. Rats were fed on a standard laboratory diet and tap water *ad libitum* and were subjected to a 12 h light–dark cycle. The dose of thiopental (50 mg kg^{-1}) was that routinely used to anaesthetize rats in our laboratory, and the dose of pentoxifylline (12 mg kg^{-1}) was the pharmacological dose used in humans. The dose of ketamine used was 80 mg kg^{-1}.

Study design

A first series of experiments was performed to assess the effects of the co-treatment with thiopental and pentoxifylline together with surgical stress and acute pancreatitis on the mortality rate in rats. In this series, 180 rats were randomly assigned to one of the following six groups, with 30 rats in each group:

- Thiopental group, which received i.p. thiopental.
- Pentoxifylline group, which received i.p. pentoxifylline.
- Thiopental + pentoxifylline group, which received i.p. thiopental and immediately after, i.p. pentoxifylline.
- Ketamine + pentoxifylline group, which received i.p. ketamine and immediately after, i.p. pentoxifylline.
- Pancreatitis + thiopental group, which received i.p. thiopental and, when anaesthesia was achieved (approximately 5–10 min after the i.p. injections), were subjected to laparotomy and infusion of 3.5% taurocholate into the biliopancreatic duct.
- Pancreatitis + thiopental + pentoxifylline group, which received i.p. thiopental and pentoxifylline and, when anaesthesia was achieved were subjected to laparotomy and infusion of 3.5% taurocholate into the biliopancreatic duct.

The lungs of those rats that died in this first series of experiments were removed for histological analysis, carried out by an experienced histologist who was unaware of the treatments.

In a second series of experiments, we assessed the effects of the co-treatment with thiopental and pentoxifylline on arterial pH and pO_2 and pCO_2 levels, grade of pulmonary oedema and pulmonary vascular permeability. To this end, 27 rats were randomly assigned to the group treated i.p. only with thiopental ($n=13$) or to the group treated i.p. with thiopental and pentoxifylline ($n=14$). Rats were maintained throughout the experiment under spontaneous ventilation with 21% FiO_2. Five to six rats per group were used to determine arterial blood gases, four per group were used to measure the grade of pulmonary oedema and another four to determine the lung permeability index. These variables were measured at 2 and 6 h after the treatments. Anaesthesia with thiopental (i.p. 50 mg kg^{-1}) was also needed at 6 h in order to obtain arterial blood and lung tissue.

A third series of experiments was performed to determine haemodynamic changes induced by the co-treatment with thiopental and pentoxifylline. Eight rats were randomly assigned to the group treated i.p. only with thiopental ($n=4$) or to the group treated i.p. with thiopental and pentoxifylline ($n=4$). Pentoxifylline was given i.p. immediately after thiopental administration. Rats were intubated *per os* with a 1.70 mm OD polyethylene catheter and ventilated with room air using a rodent ventilator (model 683, Harvard Apparatus Inc., South Natick, MA, USA) with a tidal volume of 7 ml kg^{-1}, at a rate of 80 breaths per minute. Arterial blood gases were measured during the ventilation process to maintain normal pH, pO_2 and pCO_2. A right parasternal thoracotomy and pericardiotomy were performed and the ascending aorta was carefully isolated to attach a flow-probe (Transonic Flowprobe # 2RB1087) to measure aortic blood flow (ABF) using the T206 small animal blood flow meter (Transonic Systems Inc., Ithaca, NY, USA). ABF was recorded for 90 min starting 30 min after drug administration. Mean pulmonary artery pressure (MPAP) and right ventricular end-diastolic pressure (RVEP) were measured via a catheter (OD 0.67 mm) inserted into the pulmonary artery, through the right ventricle and attached to a pressure transducer (Transpac, Abbot Critical Care Systems). The flowprobe and the transducer were connected to the T206 flow meter and MPAP, RVEP and ABF were recorded with Windaq software (Dataq instruments, Akron, OH, USA). MPAP and RVEP were recorded during the last 15 min of ABF recording. Heart rate was measured from the aortic flow recording.

Experimental model of acute pancreatitis

Animals were anaesthetized as indicated above and a 2–3 cm laparotomy was performed. Then, the biliopancreatic duct was cannulated through the duodenum and the hepatic duct was closed by a small bulldog clamp. Pancreatitis was induced by retrograde injection into the biliopancreatic duct of sodium taurocholate (3.5%) (Sigma, St Louis, MI, USA) in a volume of 1 ml kg^{-1}, using an infusion pump (Harvard Instruments), as previously described by Pereda *et al*. (2004).

Surgical procedure

In the mortality study, a 2–3 cm laparotomy was performed using sterile material. When indicated, acute pancreatitis was induced as described above. The whole surgical procedure lasted <20 min including the closure of the abdominal wound. All rats recovered from the surgical procedure a few hours (generally starting 2 h) after the induction of anaesthesia, except those receiving co-treatment with thiopental and pentoxifylline. These rats required several hours to recover, although some of them died as stated in the Results section. Post-operative care consisted of heating with a homoeothermic pad to maintain body temperature till the animal had recovered. In the study of haemodynamic parameters, a right parasternal thoracotomy and pericardiotomy were performed with the help of a Leep System 1000 (Cooper Surgical) to expose the ascending aorta. The aorta was carefully isolated to attach the flowprobe in order to measure ABF. During the haemodynamic study, care consisted of heating the animal to maintain body temperature and covering the thorax with warmed gauzes humidified with saline solution at 37°C.

Measurement of pulmonary oedema and permeability

The degree of pulmonary oedema was measured as the lung wet-to-dry weight ratio. Pulmonary vascular permeability was determined using albumin labelled with fluorescein isothiocyanate (FITC-labelled bovine serum albumin), as indicated by Gerard *et al*. (1997). At 2 h before the end of the experiment, FITC-labelled albumin (5 mg kg^{-1}) was administered via femoral vein injection. At the end of the experiment, the trachea was cannulated and the lungs lavaged *in situ* three times with saline (1 ml per lavage). The bronchoalveolar lavage fluid was collected and combined. FITC fluorescence in serum and lavage fluid was measured using a fluorescence spectrophotometer with excitation at 494 nm and emission at 520 nm. Lung permeability index was calculated as the fluorescence ratio of lavage fluid-to-blood. pO_2, pCO_2 and pH were measured in blood from aorta using an ABL700 Analyser from Radiometer Copenhagen. Histological studies of the lungs were also performed.

Histological studies

Lung pieces were rapidly removed and fixed in 10% buffered formalin. Subsequently, lung pieces were embedded in paraffin, cut and stained with haematoxylin and eosin. Assessment of tissue alterations with light microscopy was conducted by an experienced pathologist who was unaware of the treatments.

Sample size

The primary endpoint of the study was to compare mortality between both types of treatments, that is thiopental vs thiopental plus pentoxifylline. Rats (30) per group were the necessary minimum sample size. The parameters used to calculate the sample size were the following: mortality variability of 30%; α error of 5% and β error of 20%. The number of rats used in the other series was determined based on previous experimental studies performed by our group, which have shown repeatedly very low variability within the same group. The total number of animals used was 215 and they were distributed in three series of experiments as described above.

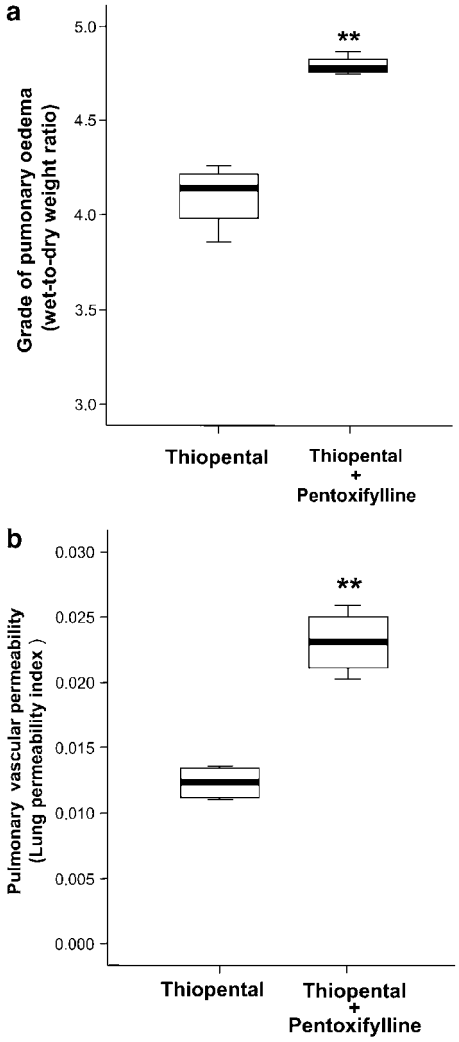

Figure 1 (**a**) Grade of pulmonary oedema and (**b**) pulmonary vascular permeability in rats treated with pentoxifylline and thiopental. The number of rats per group was four. The statistical difference is indicated as follows: $^{**}P<0.01$ vs thiopental.

Statistics

Results are expressed as median with the range and number of experiments given in parentheses; in Figures 1, 2 and 5, results are shown as box-and-whisker plots. Comparisons between experimental groups were made with the Kruskal–Wallis and Mann–Whitney *U* tests. Statistical analysis of the mortality data was carried out with the χ^2 test as well as with the Kaplan–Meier curve and log-rank test.

Results

We have found that co-treatment with pharmacological doses of pentoxifylline (12 mg kg^{-1}) and thiopental

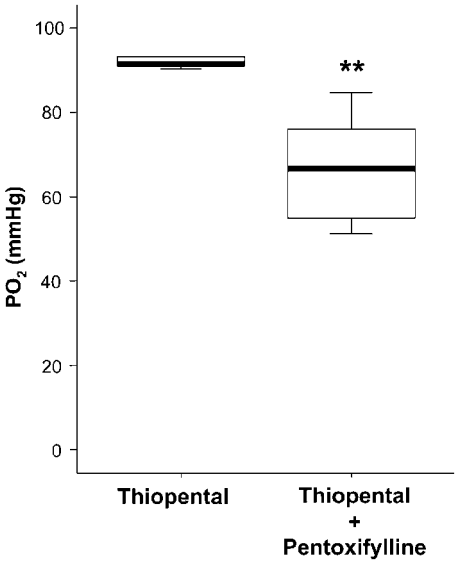

Figure 2 Arterial pO_2 in rats treated with pentoxifylline and thiopental. The number of rats per group were five to six. The statistical difference is indicated as follows: $^{**}P<0.01$ vs thiopental.

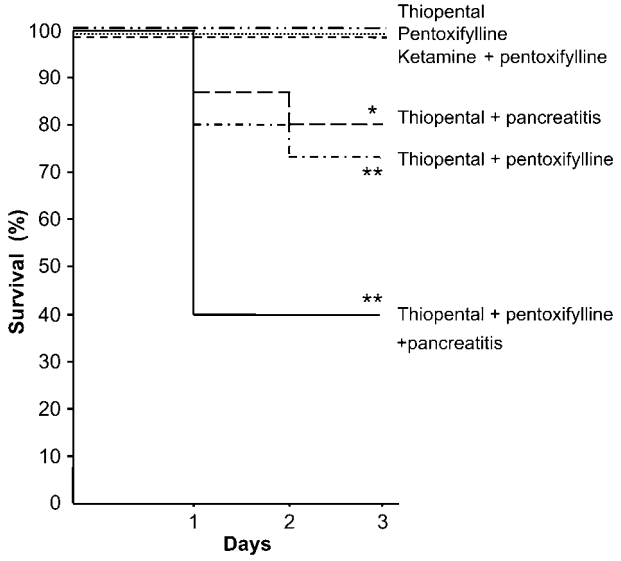

Figure 3 Kaplan–Meier survival curves of rats treated with pentoxifylline and thiopental or ketamine. The survival rate was also measured in rats with taurocholate-induced acute pancreatitis. The number of rats per group was 30. The statistical difference is indicated as follows: $^{*}P<0.05$; $^{**}P<0.01$ vs thiopental.

($50\,mg\,kg^{-1}$) i.p. causes pulmonary oedema at 2 h after the administration. The degree of pulmonary oedema was significantly higher in rats treated with pentoxifylline and thiopental than in rats treated with thiopental only (Figure 1a). Furthermore, by using albumin labelled with FITC we measured pulmonary vascular permeability at 2 h and it was significantly increased after the combined treatment than when thiopental was given alone (Figure 1b). The grade of pulmonary oedema and the lung permeability index were also increased at 6 h after the

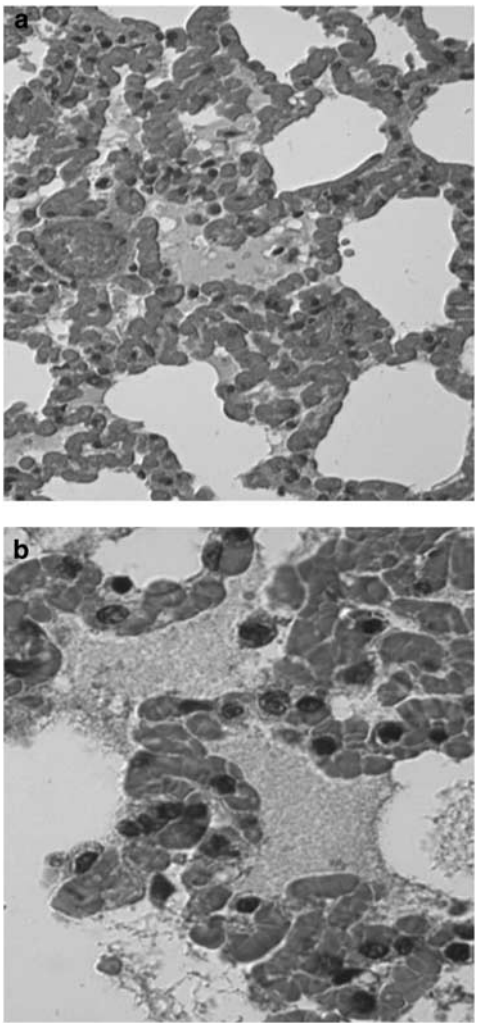

Figure 4 Histological analysis showing acute pulmonary oedema after co-administration of pentoxifylline and thiopental. Intense vascular congestion and oedema in the alveolar lumen with low inflammatory infiltrate were observed. Original magnifications were $\times 25$ for (**a**) and $\times 100$ for (**b**).

administration of thiopental and pentoxifylline (results not shown).

Arterial pO_2 did not diminish significantly at 2 h after the administration of pentoxifylline and thiopental, but it was markedly decreased at 6 h after the co-treatment when compared with rats treated with thiopental only (see Figure 2). Indeed, one third of rats that received the combined treatment suffered from hypoxemia (<60 mm Hg) at 6 h. The decrease in pO_2 was associated with a slight, but not significant, increase in pCO_2 (42.3 (40.8–51.4; $n=6$) vs 39.5 (38.2–42.1; $n=5$) mm Hg) as well as a slight, but not significant, decrease in pH (7.38 (7.36–7.41; $n=6$) vs 7.43 (7.40–7.43; $n=5$)).

We found that no deaths occurred within the first 72 h in normal rats treated with thiopental or pentoxifylline alone, but in rats treated with both thiopental and pentoxifylline, the mortality rate was 27% over this time (Figure 3). The rats receiving pentoxifylline and another anaesthesic, such as ketamine in an anaesthetic dose, showed no death (Figure 3).

The lung injury that is known to occur in acute pancreatitis (Robertson *et al*., 1988; O'Donovan *et al*., 1995; Pereda *et al*., 2004) was severely aggravated by the combined treatment with pentoxifylline and thiopental (but not with either of the drugs alone). Thus, the mortality rate in rats with taurocholate-induced pancreatitis was 20% and it was markedly increased to 60% in presence of pentoxifylline and thiopental. The histological analysis revealed that the rats treated with pentoxifylline and thiopental that died suffered from acute pulmonary oedema (Figure 4).

The pulmonary oedema induced by the co-treatment with thiopental and pentoxifylline was not caused by cardiac failure or pulmonary hypertension. Indeed, no changes in ABF or in pulmonary artery pressure were found in rats treated with thiopental and pentoxifylline when compared with those treated only with thiopental (Figure 5).

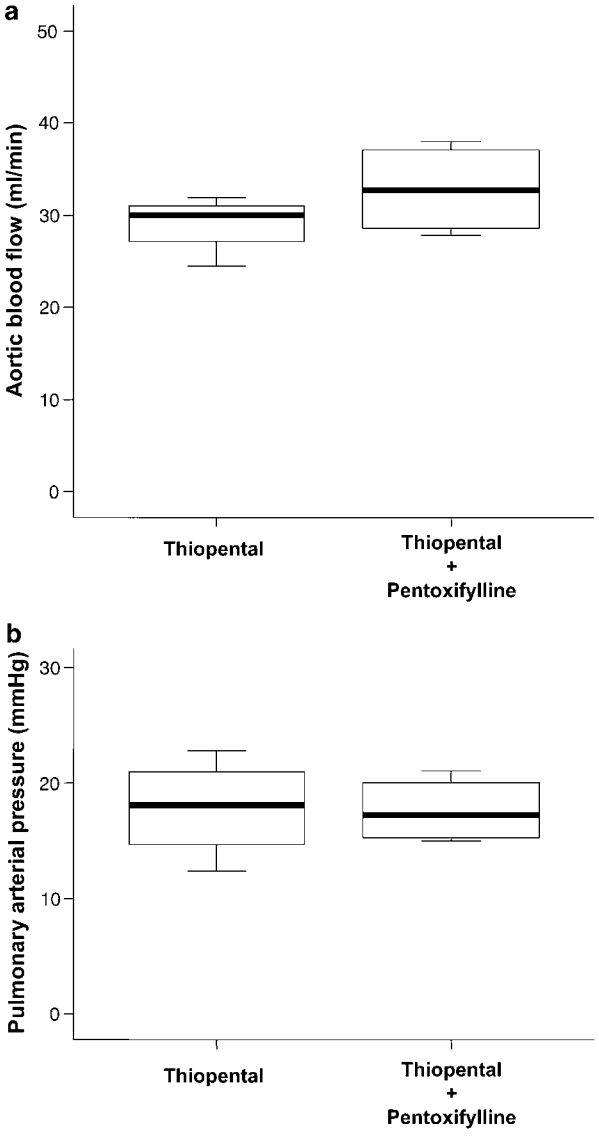

Figure 5 (**a**) ABF and (**b**) mean pulmonary arterial pressure in rats treated with pentoxifylline and thiopental. The number of rats per group was four. There was no statistical difference between groups.

Accordingly, there were no significant differences in the RVEP between these two groups (1.5 (1.0–3.0; $n=4$) mm Hg in the thiopental group vs 2.3 (1.2–2.5; $n=4$) mm Hg in the thiopental + pentoxifylline group).

Discussion

Cardiovascular and pulmonary side effects of thiopental are dose-related and other complications of injecting thiopental include allergic reactions, local tissue irritation and tissue necrosis (Reves *et al*., 2005). Thiopental produces dose-related transient central respiratory depression, and apnoea may occur during induction of anaesthesia with thiopental, but its duration is very short – around 25 s (Reves *et al*., 2005). Nevertheless, pulmonary side effects due to the association of thiopental with pentoxifylline at pharmacological doses have not been reported so far.

The dose of thiopental used was that normally used to anaesthetize rats and it is within the same range as the maximal dose recommended in human anaesthesia ($7\,mg\,kg^{-1}$) (Avram *et al*., 1993) in terms of body surface area (BSA) ($382\,mg\,m^{-2}$ in rats vs $270\,mg\,m^{-2}$ in human adults). BSA has been recommended as the main basis for drug dosage as the rate of metabolism or redistribution of a drug is proportional to metabolic rate, which in turn reflects heat losses which are generally proportional to surface area (Martindale's Pharmacopoeia, 1989; British National Formulary, 1995; Lack and Stuart-Taylor, 1997). Accordingly, BSA is often used to calculate drug doses among different species because many physiological parameters that are responsible for drug disposition, including renal function and energy expenditure, can be normalized by the use of BSA (Frazier and Price, 1998; Ambrisko and Nemeth, 2004).

Our studies were performed on laboratory rats and should be confirmed in other animal species before extrapolation to humans. To this end, *in vivo* experiments using intravenous (i.v.) injection of thiopental together with administration of pentoxifylline in species that exhibit a BSA and metabolism rate closer to those in humans would be preferred. Nevertheless, knowledge of our findings, which obviously cannot be tested directly in human subjects, may prevent similar episodes of pulmonary oedema in patients who are under treatment with pentoxifylline and who might be anaesthetised with thiopental. We feel that the increased incidence of the lethal interaction between these two widely used drugs, as shown in our experiments, should be known by the medical profession in general in order to raise awareness of an interaction that could cause serious side effects or unexpected death in some patients. Consequently, we would suggest that pentoxifylline and thiopental should not be administered simultaneously in clinical practice in order to avoid any possible risk of acute pulmonary oedema and even death in humans, until this interaction has been fully assessed in animal models.

Oliveira-Junior *et al*. (2003) did not report lethal effects after infusion of pentoxifylline in rats anesthetized with thiopental. We report here deleterious effects when these drugs were administered simultaneously. An explanation for this discrepancy is that the lethal interaction might not

occur when one of the drugs is given with a certain delay after the other. Indeed, in the paper by Oliveira-Junior *et al*. (2003) pentoxifylline was administered after surgical preparation, which consisted of tracheostomy and cannulation of the left internal carotid artery. Furthermore, in this work the dose of pentoxifylline was administered gradually by i.v. infusion over a period of 180 min.

On the other hand, co-administration of pentoxifylline and thiopental gives rise to a new experimental model of acute pulmonary oedema, which is not mediated by cardiac failure or pulmonary hypertension. Further experimental work is needed to elucidate the mechanism(s) involved in this drug interaction. It has been reported that thiopental inhibits nitric oxide (NO) synthase and consequently diminishes NO generation (Galley *et al*., 1995; Galley and Webster, 1996; Castillo *et al*., 1999), and we found that pentoxifylline also blocks NO production (Gómez-Cambronero *et al*., 2000). A complete blockade of NO production could be deleterious since NO may be protective against lung damage *in vivo*. Indeed, NO inhibits pancreatitis-induced lung injury (O'Donovan *et al*., 1995) and recently it has been reported that ventilator-induced lung injury is reduced in transgenic mice that overexpress endothelial NO synthase (Takenaka *et al*., 2006). The role of vascular endothelial growth factor (VEGF) in the interaction between thiopental and pentoxifylline could be ruled out since thiopental decreases the hypoxia-induced expression of VEGF and also the associated permeability changes in endothelial cells (Fischer *et al*., 1998).

In conclusion, our results show that simultaneous administration of pentoxifylline and thiopental at pharmacological doses causes death by acute pulmonary oedema in rats. Furthermore, co-treatment with pentoxifylline and thiopental aggravates the outcome of those disorders associated with respiratory insufficiency, such as acute pancreatitis. These findings should be taken into account in clinical practice, and consequently pentoxifylline should not be administered when anaesthesia is induced with thiopental to avoid any possible risk of acute pulmonary oedema and death in patients.

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Conflict of interest

The authors state no conflict of interest.

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