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ANESTHESIOLOGY

Respiratory Effects of the Atypical Tricyclic Antidepressant Tianeptine in Human Models of Opioid-induced Respiratory Depression

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Tianeptine is an atypical antidepressant and cognitive enhancer that can be administered orally or intravenously

ABSTRACT

Background: Animal data suggest that the antidepressant and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor modulator tianeptine is able to prevent opioid-induced respiratory depression. The hypothesis was that oral or intravenous tianeptine can effectively prevent or counteract opioid-induced respiratory depression in humans.

Methods: Healthy male and female volunteers participated in two studies that had a randomized, double blind, placebo-controlled, crossover design. First, oral tianeptine (37.5-, 50-, and 100-mg doses with 8 subjects) pretreatment followed by induction of alfentanil-induced respiratory depression (alfentanil target concentration, 100 ng/ml) was tested. Primary endpoint was ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg ($\dot{V}_E55$). Next, the ability of four subsequent and increasing infusions of intravenous tianeptine (target tianeptine plasma concentrations 400, 1,000, 1,500, and 2,000 ng/ml, each given over 15 min) to counteract remifentanil-induced respiratory depression was determined in 15 volunteers. Ventilation was measured at isohypercpania (baseline ventilation 20 ± 2 l/min). The primary endpoint was minute ventilation during the 60 min of tianeptine *versus* placebo infusion.

Results: Alfentanil reduced $\dot{V}_E55$ to 13.7 (95% CI, 8.6 to 18.8) l/min after placebo pretreatment and to 17.9 (10.2 to 25.7) l/min after 50-mg tianeptine pretreatment (mean difference between treatments 4.2 (–11.5 to 3.0) l/min, $P = 0.070$). Intravenous tianeptine in the measured concentration range of 500 to 2,000 ng/ml did not stimulate ventilation but instead worsened remifentanil-induced respiratory depression: tianeptine, 9.6 ± 0.8 l/min *versus* placebo 15.0 ± 0.9 l/min; mean difference, 5.3 l/min; 95% CI, 2.5 to 8.2 l/min; $P = 0.001$, after 1 h of treatment.

Conclusions: Neither oral nor intravenous tianeptine were respiratory stimulants. Intravenous tianeptine over the concentration range of 500 to 2000 ng/ml worsened respiratory depression induced by remifentanil.

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This article is featured in "This Month in Anesthesiology," page A1. This article has a video abstract. This article has a visual abstract available in the online version. H.A. and R.v.d.S. contributed equally to this article.

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- Tianeptine may cause respiratory stimulation during opioid-induced respiratory depression by enhancing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated transmission and reducing glutamatergic transmission at *N*-methyl-d-aspartate receptors
- However, tianeptine also acts as a μ-opioid receptor agonist, which may reduce its respiratory stimulatory capabilities

What This Article Tells Us That Is New

- The hypothesis that tianeptine is able to cause effective reversal of opioid-induced respiratory depression was tested in 15 male and female subjects in a double-blind, randomized, placebo-controlled crossover study by determining the effect of tianeptine at four increasing target plasma concentrations on remifentanil-induced respiratory depression at isohypercapnia
- Over the plasma tianeptine concentration range tested (500 to 2,000 ng/ml), it did not produce respiratory stimulation during remifentanil-induced respiratory depression but instead worsened respiratory depression with a further decline in ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg by 5 l/min

Modern medicine relies heavily on opioids for suppression of moderate to severe pain. Strong opioids are used during anesthesia to suppress autonomic responses and are given for treatment of acute (postoperative) pain, chronic cancer pain and noncancer pain.[1] However, the use of opioids comes with adverse effects, of which opioid-induced respiratory depression is most problematic, as it is potentially lethal.[2] Opioid-induced respiratory depression is related to depression or inactivation of respiratory rhythm generation within the brainstem due to activation of μ-opioid receptors predominantly in the pre-Bötzinger complex and Kölliker–Fuse nucleus.[3–5] One way of treating or preventing opioid-induced respiratory depression without compromising analgesia is by administration of respiratory stimulants that do not interfere with the opioid receptor system.[6] Many such stimulants are currently being developed; however, none seem adequate for therapeutic use, and all need further study of efficacy and toxicity.[6]

A possible novel option for respiratory stimulation could be the administration of tianeptine.[7] Tianeptine is an atypical antidepressant and cognitive enhancer that can be administered orally or intravenously. It induces neuroplastic changes and modulates noradrenergic, dopaminergic, and glutamatergic pathways.[8–10] For example, tianeptine facilitates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated glutamatergic transmission and reduces AMPA receptor surface diffusion. AMPA receptors are present in key brainstem centers involved in respiratory drive, such as the pre-Bötzinger complex, where they play an important role in the maintenance of respiratory rhythmogenesis and inspiratory drive, as well as sites outside the pre-Bötzinger complex.[2–6] One animal study that investigated the respiratory effects of tianeptine on morphine-induced respiratory depression showed that tianeptine pretreatment prevented opioid-induced respiratory depression without affecting antinociception.[7] Tianeptine is marketed currently in a number of countries, primarily as an antidepressant,[11] and consequently is a practical target for study as a reversal agent of opioid-induced respiratory depression. Moreover, the ampakines are among the most effective respiratory stimulants.[6] An important additional observation is that tianeptine is an agonist at the μ-opioid receptor,[12] making it an even more attractive candidate as a respiratory stimulant drug, because it may enhance pain relief while stimulating respiration.

The current study explored a possible therapeutic role for tianeptine in mitigating opioid-induced respiratory depression. In a first proof-of-concept study (study 1), we tested oral tianeptine on alfentanil-induced respiratory depression by measuring the hypercapnic ventilatory response. Next, we chose to further study intravenous tianeptine, as the intravenous route was deemed more clinically relevant when aiming at reversal of opioid-induced respiratory depression in the perioperative setting (study 2). In study 2, we first studied the pharmacokinetics of intravenous tianeptine in six healthy volunteers (study 2a). Using data from this initial population pharmacokinetic modeling study, we designed a tianeptine dose-escalating study to determine the effect of tianeptine on top of remifentanil-induced respiratory depression (study 2b). Both studies 1 and 2b had double-blind, randomized, placebo-controlled crossover designs. Our hypothesis was that in study 1, we would detect a signal that tianeptine is able to counteract opioid-induced respiratory depression and that study 2 would show that tianeptine is able to cause effective reversal of opioid-induced respiratory depression.

Materials and Methods

Ethics, Registration, and Changes in Study Protocol

The study protocols were approved by the institutional review board (METC [Medisch Ethische Toetsingscommissie] Leiden-Den Haag-Delft) in Leiden and the Central Committee on Research Involving Human Subjects (CCMO [Centrale Commissie Mensgebonden Onderzoek], competent authority) in The Hague, both in The Netherlands. All study procedures were conducted according to good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki. Before enrollment, all subjects gave written informed consent, after which their medical history was taken and a physical examination was performed. Study 1 was performed from January to July 2014, and the pharmacokinetic studies 2a and 2b started in June 2019 and were completed in January 2021. All studies were registered in the trial register of the Dutch Cochrane Center (www.trialregister.nl) under identifiers NL3849

(study 1) and NL7907 (study 2) with principle investigator Albert Dahan, M.D., Ph.D., and registration dates August 21, 2013 and July 26, 2019 for studies 1 and 2, respectively. Study 1 was exploratory and served to detect a clinically relevant reduction in alfentanil-induced respiratory depression (tianeptine effect is greater than the placebo effect; no *a priori* significance level was defined). Once an increase in minute ventilation was detected with 50 mg of tianeptine, we proceeded with a second study that determined the pharmacokinetics of intravenous tianeptine and the effect of escalating tianeptine doses on remifentanil-induced respiratory depression.

Study 1 initially had four dosing groups: 37.5, 50, and 100 mg of oral tianeptine to counteract alfentanil-induced respiratory depression at a target plasma concentration of 100 ng/ml and 100 mg of oral tianeptine to counter alfentanil respiratory effect at an alfentanil target plasma concentration of 50 ng/ml. After completion of three doses (37.5 mg of tianeptine + 100 ng/ml alfentanil, 50 mg of tianeptine + 100 ng/ml of alfentanil, and 100 mg of tianeptine + 50 ng/ml alfentanil), the study was prematurely ended. After the oral tianeptine study had demonstrated a clinically relevant effect, we developed an intravenous administration form of the drug as the intravenous route was considered more clinically relevant when aiming at reversal of opioid-induced respiratory depression in the perioperative setting. The second study had two parts: an initial population pharmacokinetic modeling study to obtain pharmacokinetic data to design an infusion scheme for study 2b, in which the effect of four sequential increases in tianeptine doses were given on top of remifentanil-induced respiratory depression and minute ventilation ($\dot{V}_E$) was measured at isohypercapnia.

Participants

Male and female participants were recruited by advertisements in the local newspaper and flyers posted on the campus of Leiden University. Inclusion criteria were: age 18 to 40 yr; body mass index of less than 30 $kg \cdot m^{-2}$; and the ability to communicate with the investigators. Exclusion criteria were: clinically relevant history or current physical or mental disease; systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 95 mmHg at screening; history of alcohol or substance abuse within 3 yr before screening; use of more than 20 units of alcohol per week; a positive alcohol breath test at screening or on the morning of the dosing days; use of any medication except oral contraceptives; not using contraceptives or not surgically sterilized when sexually active; positive pregnancy test at screening or on the morning of the study; history of allergic reaction to study medication; participation in an investigational drug trial in the 2 months before screening; or any other condition that in the opinion of the investigator would complicate or compromise the study or the well-being of the subject.

Study Design

To measure $\dot{V}_E$ and induce isohypercapnia in studies 1 and 2b, we used the dynamic end-tidal forcing technique.[13,14] This technique allows rapid changes in end-tidal carbon dioxide concentration while maintaining the end-tidal oxygen concentration constant. The technique has been described extensively before. In brief, subjects breathed through a facemask connected to a pneumotachograph (catalog no. 4813; Hans Rudolph Inc., USA) to measure respiratory flow and volume, which was connected to three mass flow controllers (Bronkhorst High Tech, The Netherlands) for the delivery of oxygen, carbon dioxide, and nitrogen. The mass flow controllers were controlled by a computer running the custom-made RESREG/ACQ software (Leiden University Medical Center, The Netherlands), allowing the manipulation of the end-tidal gas concentrations by varying the inspired concentration, breath-to-breath data acquisition and real-time visualization of the data. The inspired and expired oxygen and carbon dioxide partial pressures were measured at the mouth using a capnograph (Datex Capnomac, Finland). Heart rate, blood pressure, and arterial oxygen saturation were continuously measured from the arterial cannula (Datex Cardiocap, Finland), and by pulse oximetry (Masimo Corporation, USA), respectively.

Study 1. For study 1, a total of 24 subjects received alfentanil/tianeptine or alfentanil/placebo in a double-blind, randomized, crossover design with eight subjects receiving each tianeptine dose. The steady-state respiratory response to hypercapnia was measured using four 7-min steps in end-tidal carbon dioxide concentration were applied with step sizes of 4.5 mmHg (0.6 kPa), 9 mmHg (1.2 kPa), 13.5 mmHg (1.8 kPa), and 18.0 mmHg (2.4 kPa) above resting end-tidal carbon dioxide concentration.[14] Throughout the test, the end-tidal P_{O_2} was kept at normoxia (105 mmHg or 14 kPa). The hypercapnic ventilatory response was obtained before any drug administration and 15 min after ingestion of the tianeptine or placebo tablets; alfentanil target-controlled infusion (targets 100 or 50 ng/ml) started 45 min after tianeptine or placebo tablets, and subsequent hypercapnic ventilatory responses were obtained at 30, 90, and 150 min during alfentanil administration. A final hypercapnic ventilatory response was obtained 30 min after discontinuation of the alfentanil infusion. The design of the study considered the kinetics of oral tianeptine with rapid absorption (maximum concentration occurs after approximately 1 h), systemic availability of 99%, and an elimination half-life of 2.5 h.[15] The primary endpoint for analysis was the change from baseline of $\dot{V}_E$ at an extrapolated end-tidal carbon dioxide concentration of 7.3 kPa or 55 mmHg ($\dot{V}_E55$). Since bioavailability may vary due to alfentanil-induced delayed gastric emptying, a pragmatic approach was adopted for data analysis. In the analysis, we used the maximum change in $\dot{V}_E55$ value (relative to baseline) of the three measurements during alfentanil infusion

observed in the tianeptine group and compared this measurement to the corresponding measurement during the placebo experiment.

The Hypercapnic Ventilatory Response. The ventilatory response to hypercapnia (fig. 1) has a "dog leg" or hockey stick appearance with an initial flat part, where ventilation is independent of the carbon dioxide concentration, and, beginning at the so-called ventilatory recruitment threshold, a linear increasing part.[14,16] The linear increase is described by a slope (S) and an "apneic threshold" (B) or the extrapolated carbon dioxide concentration at which ventilation theoretically would be 0, defined by the following equation: ventilation = S × (end-tidal carbon dioxide concentration − B). Only during anesthesia does ventilation reach 0 at the apneic threshold; hence, the flat part is considered the wakefulness drive to breathe. Upon administration of an opioid, the linear part of the curve often shifts to the right, causing a prolongation of the flat part of the curve. This is apparent in figure 1A and B, which show that ventilation does not increase going from 5 to 6 kPa (fig. 1A) or from 6 to 7 kPa (fig. 1B).

Pharmacokinetic Study (Study 2a). The pharmacokinetics of intravenous tianeptine (AMO Pharma Ltd., United Kingdom) was measured in six subjects. *In silico* simulations were performed based on the pharmacokinetic data set of Salvadori *et al.*[15] to obtain four 15-min steps in tianeptine plasma concentration with escalation concentrations: 100, 200, 400, and 800 ng/ml. The simulations led to a specific dosing scheme in the pharmacokinetic study: a bolus dose given over 1 min followed by a 14-min continuous infusion. The first dose (t = 0) was 2 mg followed by an infusion of 0.7 mg given over 14 min (rate = 0.05 mg/min). After 15 min, a 2-mg bolus dose was followed by 1.4 mg over 14 min (0.10 mg/min). After 30 min, a 4-mg bolus was followed by 2.8 mg given over 14 min (0.2 mg/min). Finally, a bolus dose of 8 mg at t = 45 min was followed by an infusion of 5.6 mg over 14 min (0.4 mg/min). The total dose given was 26.5 mg. All doses were based on a 70-kg individual.

Study 2b. In study 2b, 15 subjects participated in a double-blind, randomized, crossover design receiving remifentanil/placebo or remifentanil/tianeptine. The effect of an intravenous tianeptine dose escalation on remifentanil-induced respiratory depression at isohypercapnia was measured. To that end, the end-expired end-tidal carbon dioxide concentration was increased such that $\dot{V}_E$ was 20 ± 2 l/min. Thereafter, remifentanil was infused by target-controlled infusion, such that isohypercapnic $\dot{V}_E$ decreased by approximately 40% of baseline. After steady-state $\dot{V}_E$ was reached, tianeptine or placebo was infused at four distinct target levels for 15 min each (total duration of infusion = 60 min) with target steady-state tianeptine plasma concentrations of 400, 1,000, 1,500, and 2,000 ng/ml. Breath-to-breath minute $\dot{V}_E$ was measured (in min) and analyzed.

Blinding, Dispensing, and Randomization. Both studies were fully blinded and randomized. Randomization was performed by the trial pharmacy using computer-generated randomization lists. After subject allocation, the Leiden University Medical Center trial pharmacy prepared the medication on the morning of the study. For study 1, all tablets were reencapsulated, with all capsules identical in

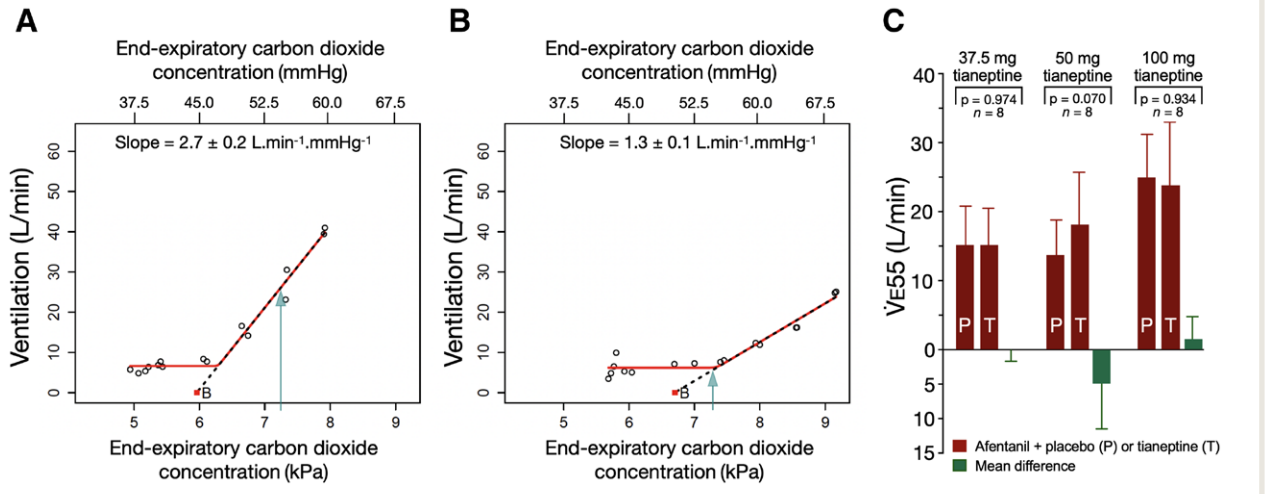

Fig. 1. Effect in study 1 of 50 mg of oral tianeptine (*A*) and placebo (*B*) on the steady-state ventilatory response to carbon dioxide in a single subject from a single run 90 min after the ingestion of tianeptine or placebo. The *arrow* indicates ventilation at an extrapolated end-expiratory concentration of 7.3 kPa or 55 mmHg ($\dot{V}_E$55). The *dots* represent 1-min averages of ventilation data obtained at rest (no added carbon dioxide; horizontal part of the *red curve*) or at elevated end-expiratory carbon dioxide concentration. The *black broken curve* is the fitted hypercapnic ventilatory response curve. The data at ventilation levels above resting ventilation are fitted to the following equation: Ventilation = slope × (end-tidal carbon dioxide concentration − B). (*C*) Pooled data of the primary endpoint of study 1: $\dot{V}_E$55. The *red bars* show the effects of either alfentanil plus placebo (P) or alfentanil plus tianeptine (T) for each of the three dosing groups. The mean differences are given in green. The data are means ± 95% CI.

size and color. For study 2b, the intravenous tianeptine or placebo were delivered in an opaque syringe for intravenous administration. The study drugs were packed in numbered (subject number) but otherwise unmarked containers or syringes and dispensed to the study team just before dosing. The study was independently monitored, and data analyses were performed after database lock.

Drug Development, Opioid, and Tianeptine Administration. In study 1, alfentanil (Jansen Cilag BV, The Netherlands; alfentanil HCl in 0.9% NaCl in water) was administered *via* an infusion cannula placed in the left or right cubital vein. The drug was administered by target-controlled infusion with a target plasma concentration of 50 or 100 ng/ml (on different occasions) using the pharmacokinetic data set from Maitre *et al*.[17] At 45 min after the ingestion of the tianeptine/placebo (37.5, 50, or 100 mg), the alfentanil infusion started and lasted for 2 h. Over this time range, we estimated that the plasma concentrations after the 37.5-mg oral tianeptine dose rapidly decrease from 500 to 180 ng/ml and after the 50-mg oral tianeptine dose decrease from 700 to 260 ng/ml.[15] Tianeptine was ingested with 100 ml of noncarbonated water. Tianeptine tablets (Stablon, 12.5 mg) were obtained from Laboratories Servier SA (France).

For studies 2a and 2b, a sterile tianeptine sodium intravenous formulation (sodium; 7-[(3-chloro-6-methyl-5,5-dioxo-11Hbenzo[c][2,1] benzothiazepin-11-yl)amino] heptanoate; 1 mg/ml) was developed by AMO Pharma Ltd. Tianeptine is a drug with two pKa values. Formulation approaches therefore sought to optimize the pH where ionization would afford physical stability at the target drug loading, without pH-mediated chemical instability. Drug loading optimization also addressed hydrophobic stacking instability concerns. The resulting formulation was manufactured under current Good Manufacturing Practice conditions by KABS Pharmaceuticals Inc. (Canada) with AMO Pharma Ltd. oversight. Sterility and bacterial endotoxin testing were performed by Nucro-Technics Inc. (Canada). Full current Good Manufacturing Practice release testing was performed by KABS Pharmaceuticals Inc. (Canada) using validated methods. Clinical labeling, packaging, and qualified person release were performed by the Leiden University Medical Center pharmacy, which is current Good Manufacturing Practice-certified.

In study 2b, remifentanil (Sandoz NV, Belgium) was infused by target-controlled infusion, using the pharmacokinetic set of Minto *et al*,[18] after $\dot{V}_E$ had stabilized at its isohypercapnic level of 20 ± 2 l/min. Remifentanil infusion was started at a target concentration of 1 ng/ml and was adjusted in steps of 0.1 ng/ml to reach a ventilatory depression level of 40% of baseline. Only when remifentanil-depressed $\dot{V}_E$ had reached its target steady-state level, did the tianeptine infusion start. Four consecutive dose escalations in tianeptine were performed at 15-min intervals to reach estimated steady-state tianeptine target concentrations of 400, 1,000, 1,500, and 2,000 ng/ml. This was done by administration of a bolus dose given over 1-min followed by a 14-min continuous infusion. The doses were determined based on the results of the pharmacokinetic study. The first dose was made up of a 4-mg bolus, given over 1 min, followed by 2.8 mg given over 14 min, with a subsequent dose increment of an 8-mg bolus, followed by 5.6 mg given over 14 min; the next incremental bolus dose was 9 mg, followed by 6.3 mg given over 15 min and finally a 10-mg bolus followed by 7 mg given over 14 min. Each bolus infusion lasted 1 min, and all doses are per 70 kg.

Blood Samples and Measurement of Tianeptine and MC5. In study 2a and 2b, blood samples were obtained from an arterial line, placed in the radial artery of the nondominant arm, to measure plasma concentrations of tianeptine and its metabolite MC5. Blood samples were obtained at t = 0 (pre-tianeptine baseline), and 1, 2, 9, 15, 16, 17, 24, 30, 31, 32, 39, 45, 46, 47, 54, 60, 61, 62, 70, 80, and 90 min after the start of tianeptine infusion. Plasma samples were shipped to Charles River Laboratories Montreal ULC (Canada), where the concentrations were measured by liquid chromatography-tandem mass spectrometry. The analytical range for both parent and metabolite was 1 to 1,000 ng/ml. The intraassay precision and bias were no greater than 6 and −11%, respectively, while the interassay precision and bias were no greater than 5 and − 6%, respectively, over the concentration range of 1 to 1,000 ng/ml for tianeptine and MC5.

Adverse Events. All adverse events were noted in the case report forms. Despite the fact that the literature indicates that tianeptine, even at high doses, is well tolerated, all subjects were closely monitored during tianeptine exposure and queried after finalizing the experiment with special focus on dry mouth, dizziness, drowsiness, and postural hypotension.

Sample Size and Data Analysis

Sample Size Determination. Because study 1 was a proof-of-concept study, the number of subjects was somewhat arbitrarily set at $n = 8$ per dose arm. The aim of this part of the project was to detect a clinically relevant reduction in alfentanil-induced respiratory depression after the ingestion of tianeptine with *a priori* definition of effects size or significance level. In study 2b, no data were available on the effect of intravenous tianeptine on remifentanil-induced respiratory depression. We therefore relied on earlier studies from our laboratory on the effect of the intravenous infusion of the experimental drug GAL021 (currently known as ENA001) and *S*-ketamine on reversal of opioid respiratory effects.[19,20] In those randomized controlled trials that used a crossover design, 12 subjects were sufficient to detect a significant reversal effect from the interventions. To consider the uncertainties in our assumptions, we performed the randomized controlled trial in 15 subjects using a crossover design (placebo *vs.* tianeptine; each subject underwent two experiments with at least 1 week between visits).

Data Analysis of Study 1. The slope of the hypercapnic ventilatory response was estimated in R (The R Foundation for Statistical Computing, www.r-project.org). Within R, data analysis was automated: (1) from the raw data, the medians of the 1-min breath-to-breath minute $\dot{V}_E$ were calculated; (2) all measurements obtained without carbon dioxide stimulation (baseline $\dot{V}_E$) and measurements during the final 2-min of each hypercapnic step of the hypercapnic ventilatory response, representing steady-state hypercapnic $\dot{V}_E$, were selected for further analysis; and (3) the linear increasing parts of the hypercapnic ventilatory response curves beyond the ventilatory recruitment threshold were fitted ($\dot{V}_E$ *vs.* end-tidal carbon dioxide concentration) to obtain the slope of the hypercapnic ventilatory response curve and the extrapolated $\dot{V}_E55$.[14]

A two-way repeated-measures analysis of variance (with factors treatment, time, and time × treatment) was run for each tianeptine dose to determine the effect of tianeptine *versus* placebo on $\dot{V}_E55$. Since this was a proof-of-concept trial aimed to detect an exploratory study, no *P* value was determined *a priori* for statistical significance. Statistical analysis was performed in R.

Data Analysis of the Pharmacokinetic Study (Study 2a). The pharmacokinetic data were analyzed with a two-compartment pharmacokinetic model using a population analysis in NONMEM version 7.5.0 (ICON Development Solutions, USA). The pharmacokinetic model estimates were used to design the dosing scheme used in study 2.

Data Analysis of Study 2b. Eight 1-min timepoints were defined: timepoint A = baseline, before hypercapnia and drug administration; timepoint B = isohypercapnia, before any drug administration); timepoint C = remifentanil at steady-state, before tianeptine administration; timepoint D = 15 min into tianeptine administration, *i.e.,* end of first tianeptine step with target concentration of 400 ng/ml; E = 30 min into tianeptine administration, *i.e.* end of second tianeptine step with target steady-state concentration 1,000 ng/ml; F= 45 min into tianeptine administration, *i.e.* end of third tianeptine step with target concentration 1,500 ng/ml; G = 60 min into tianeptine administration, *i.e.* end of last tianeptine step with target concentration 2,000 ng/ml; and H = 15 min after the end of tianeptine infusion. At each time point, 1-min averages were obtained of minute $\dot{V}_E$, tidal volume, and respiratory rate for data presentation. The minute $\dot{V}_E$ data (tianeptine *vs.* placebo over time) were analyzed by a two-way repeated-measures analysis of variance (with factors treatment, time, and time × treatment) in R with *P* values < 0.01 considered significant to correct for multiple comparisons (5). *Post hoc* tests were by two-tailed paired *t* tests. The data are means ± SD unless otherwise stated.

Results

All subjects completed the experimental sessions without serious adverse events. Apart from sedation, no adverse events were detected. Altogether, 45 healthy subjects (22 men and 23 women) participated with a mean age of 23 yr (range, 20 to 26 yr) and a mean body mass index of 23 kg/m^2 (range, 20 to 26 kg/m^2).

Study 1

An example of a placebo and tianeptine experiment after the oral ingestion of 50 mg of tianeptine or placebo in a single subject is shown in figure 1. It shows that alfentanil e 50-$\dot{V}_E55$ after thmg tianeptine pretreatment was greater than that after placebo pretreatment (26.4 l/min *vs.* 5.8 l/min) due to an increase in the slope of the hypercapnic ventilatory response curve and a leftward shift of the hypercapnic ventilatory response curve. The placebo curve is typical for an opioid effect, *i.e.* a rightward shift of the ventilatory response curve and a decrease of the slope (see fig. 1).[14]

Population analysis of the studentized residuals showed that there was normality, as assessed by the Shapiro–Wilk test of normality and no outliers, as assessed by nonstudentized residuals greater than 3 standard deviations. There was sphericity for the interaction term, as assessed by Mauchly's test of sphericity for each of the analyzed tianeptine doses. There was no statistically significant interaction between tianeptine or placebo and time on alfentanil-induced decrease in $\dot{V}_E55$ for 37.5 mg of tianeptine (n = 8; mean difference, –0.1 l/min; 95% CI, –1.7 to 1.5 l/min; P = 0.974). Tianeptine (50 mg) had a more pronounced effect on $\dot{V}_E55$: alfentanil reduced $\dot{V}_E55$ to 13.7 l/min (95% CI, 8.6 to 18.8 l/min) after placebo pretreatment and to 17.9 l/min (95% CI, 10.2 to 25.7 l/min) after 50-mg tianeptine pretreatment (n = 8; mean difference, 4.2 l/min; 95% CI, –11.5 to 3.0 l/min; P = 0.070; fig. 1C). We considered this ventilatory effect to be the signal that we were looking for. For the group treated with 100 mg of tianeptine and 50 ng/ml alfentanil, no effect on $\dot{V}_E55$ was observed; the interaction between tianeptine and alfentanil was not significant (n = 8; mean difference, 1.5 l/min; 95% CI, –1.8 to 4.8 l/min; P = 0.934).

Pharmacokinetic Study 2a

The mean plasma concentration of tianeptine and its metabolite TMC5 are given in figure 2A. On average, the measured steady-state tianeptine concentrations were within the target ranges as determined by the *in silico* simulation studies based on the pharmacokinetic data set of Salvadori *et al.*[15] The data fits are given in figure 3. They show the measured concentrations (closed circles) and data fit (continuous lines). Population parameter estimates derived from the NONMEM analysis were as follows: volume of compartment 1 (V_1) ± standard error of the estimate 1.5 ± 0.5 l, ω^2 (with between-subject variability in the log domain) = 0.17 ± 0.26; volume of compartment 2 (V_2) = 13.2 ± 1.2 l, with ω^2 = 0.02 ± 0.01; elimination clearance (CL_1) = 16.0 ± 1.0 l/h, with ω^2 = 0.002 ± 0.006; and intercompartmental clearance (CL_2) = 68.5 ± 25.3 l/h,

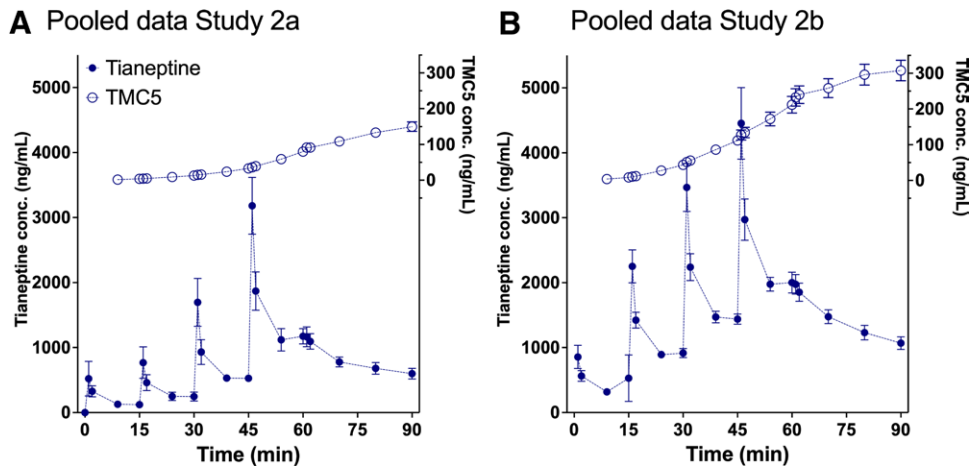

Fig. 2. Results of study 2a and 2b. (*A*) Study 2a. Plasma concentrations of tianeptine and its metabolite TMC5 in the pharmacokinetic study were obtained in six subjects with a dosing regimen based on the pharmacokinetic data from Salvadori *et al.*[15] (*B*) Study 2b. Plasma concentrations of tianeptine and its metabolite TMC5 observed during the randomized placebo-controlled trial in 15 subjects. The data are means ± 95% CI.

with $\omega^2 = 0.14 \pm 0.15$. Finally, σ^2 (with in-subject variability in the log domain) $= 0.014 \pm 0.003$. Using these data, a new infusion scheme was designed starting with an initial 15-min target steady-state tianeptine concentration of 400 ng/ml, followed by 1,000, 1,500, and 2,000 ng/ml.

Study 2b.

The mean plasma concentration of tianeptine and its metabolite TMC5 are given in figure 2B. Average measured steady-state tianeptine plasma concentrations were 530, 917, 1,440, and 2,000 ng/ml. Baseline end-tidal carbon dioxide concentration did not differ between treatment arms: placebo (mean ± SD), 5.2 ± 0.6 kPa (39 ± 4 mmHg) *versus* tianeptine, 5.2 ± 0.8 kPa (39 ± 6 mmHg). The end-tidal carbon dioxide concentration values at the initiation of the isohypercapnic clamp were: placebo, 6.7 ± 0.6 kPa (50 ± 5 mmHg) *versus* tianeptine, 6.6 ± 0.6 kPa (49 ± 5 mmHg); at the end of the experiment, the equivalent values were as follows: placebo, 6.7 ± 0.6 kPa (50 ± 5 mmHg) *versus* tianeptine, 6.7 ± 0.7 kPa (50 ± 5 mmHg). To get an indication of end-tidal carbon dioxide concentration control, we calculated the SD of end-tidal carbon dioxide concentration during a random 10-min period of the isohypercapnic clamp. These SD values were, on average, 0.06 and 0.08 kPa (0.45 and 0.60 mmHg) in the placebo and tianeptine arms of the study or 1 and 1.2% of the target end-tidal CO_2 concentrations, respectively. The remifentanil target concentrations did not differ between the placebo and tianeptine arms of the study and ranged from 0.7 to 2.0 ng/ml in the two arms.

Examples of placebo and tianeptine experiments in one subject (subject 001) are given in figure 4. The figure shows the breath-to-breath data (black dots). The difference between the two treatments is evident, with a slow tianeptine-induced further decline in $\dot{V}_E$ relative to placebo data. The mean ventilatory data are presented in figure 5. It shows that (1) isohypercapnia increased $\dot{V}_E$ to 23.2 ± 3.0 l/min (placebo) and 21.6 ± 2.6 l/min (tianeptine); (2) remifentanil decreased $\dot{V}_E$ by 40% in both groups; (3) placebo had no effect on $\dot{V}_E$ that remained constant at approximately 15 l/min throughout the last hour of the study (periods C through G: from 14.9 ± 0.5 to 15.0 ± 0.9 l/min); and (4) tianeptine infusion caused a further decrease in $\dot{V}_E$ from period C to G, from 14.2 ± 0.4 to 9.6 ± 0.8 l/min, a 35% decrease (fig. 5).

Analysis of the studentized residuals showed that there was normality as assessed by the Shapiro–Wilk test of normality and no outliers, as assessed by no studentized residuals greater than ± 3 SDs. There was sphericity for the interaction term, as assessed by Mauchly's test of sphericity. There was a statistically significant interaction between treatment and time on $\dot{V}_E$ ($P < 0.001$). Therefore, simple main effects were run. At the end of the 15-min remifentanil infusion, $\dot{V}_E$ was not statistically significantly different for the placebo condition (14.9 ± 0.5 l/min) compared to the tianeptine condition (14.2 ± 0.4 l/min) just before tianeptine or placebo infusion (mean difference, 0.6 l/min, 95% CI, –0.5 to 1.6 l/min; $P = 0.262$; fig. 5B, timepoint C). Next, $\dot{V}_E$ decreased after 15 min of tianeptine infusion (13.9 ± 0.4 l/min) compared to the placebo (15.4 ± 0.5 l/min; mean difference, 1.4 l/min; 95% CI, 0.1 to 2.8 l/min; $P = 0.040$; fig. 5B, timepoint D) and after 30 min of tianeptine infusion (12.1 ± 0.6 l/min) compared to placebo (14.5 ± 0.6 l/min; mean difference, 2.4 l/min; 95%

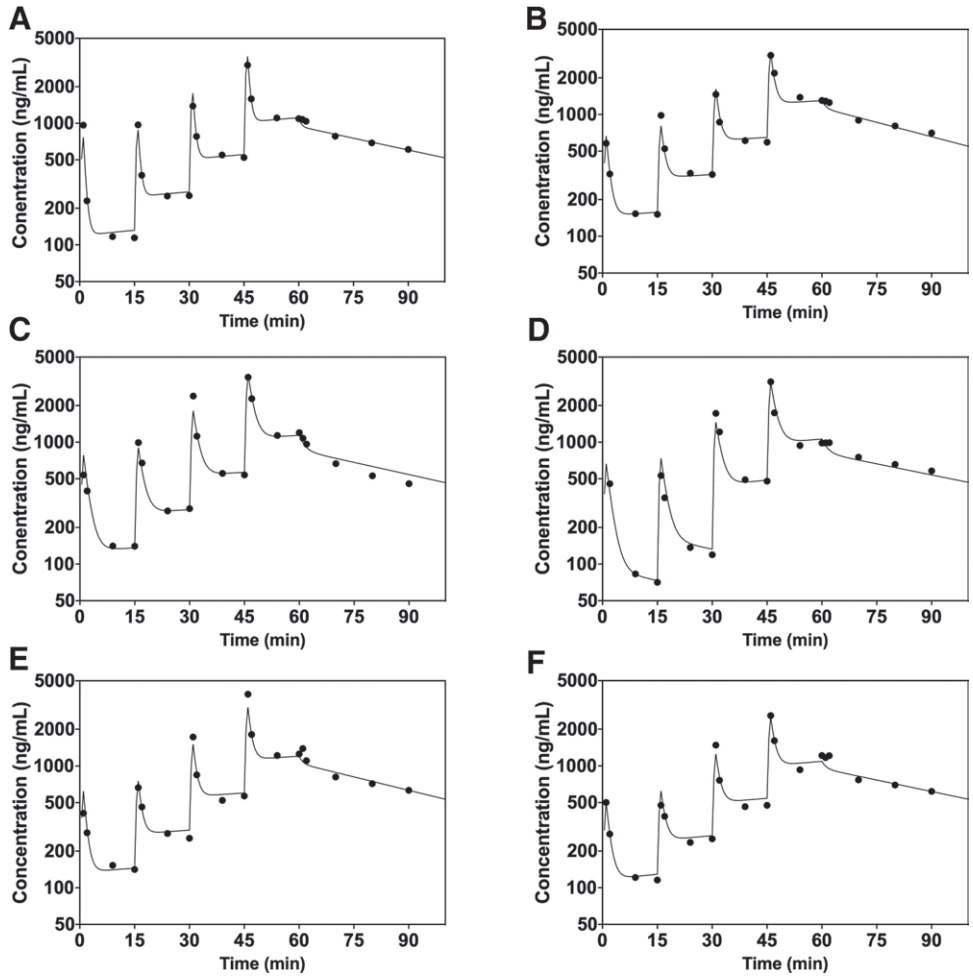

Fig. 3. NONMEM data fits of the pharmacokinetic study in six subjects (*A–F*) treated with a tianeptine infusion scheme based on the pharmacokinetic data set of Salvadori *et al.*[15] (study 2a). The estimated pharmacokinetic model parameters were used to design the infusion scheme of study 2b.

CI, 0.5 to 4.2 l/min; $P = 0.016$; fig. 5B, timepoint E). When correction for multiple comparisons was applied (P values $< 0.01 = 0.05/5$), $\dot{V}_E$ was significantly decreased after 45 min of tianeptine infusion (11.3 ± 0.5 l/min) compared to the placebo (14.4 ± 0.5 l/min; mean difference, 3.1 l/min; 95% CI, 1.8 to 4.4 l/min; $P < 0.001$; fig. 5B, timepoint F), 60 min of tianeptine infusion (9.6 ± 0.8 l/min) compared to the placebo (15.0 ± 0.9 l/min; mean difference, 5.3 l/min; 95% CI, 2.5 to 8.2 l/min; $P = 0.001$; fig. 5B, timepoint G) and remained decreased at 15 min after discontinuation of tianeptine infusion (10.3 ± 0.7 l/min) compared to the placebo (15.5 ± 0.7 l/min; mean difference, 5.2 l/min; 95% CI, 3.7 to 6.7 l/min; $P < 0.001$; fig. 5B, timepoint H). $\dot{V}_E$ did not change over time in the placebo condition ($P = 0.391$), whereas $\dot{V}_E$ did significantly decrease over time for the tianeptine condition from the start of infusion ($P < 0.001$).

Discussion

The main finding of our randomized controlled trial (study 2b) is that over the concentration range tested (500 to 2,000 ng/ml), tianeptine did not produce respiratory stimulation during remifentanil-induced respiratory depression but instead worsened respiratory depression with a further decline in $\dot{V}_E$ by 5 l/min (fig. 5). The rejection of our hypothesis deserves in-depth scrutiny of the drug, the animal data, and the various steps taken in our project.

Pharmacology of Tianeptine

Tianeptine has structural similarities to the tricyclic antidepressants but has no affinity for neurotransmitter receptors and does not interfere with monoaminergic modulators in the brain.[8,9,11] It has two metabolites: MC5, which is the main metabolite in plasma, and MC3, which is the main

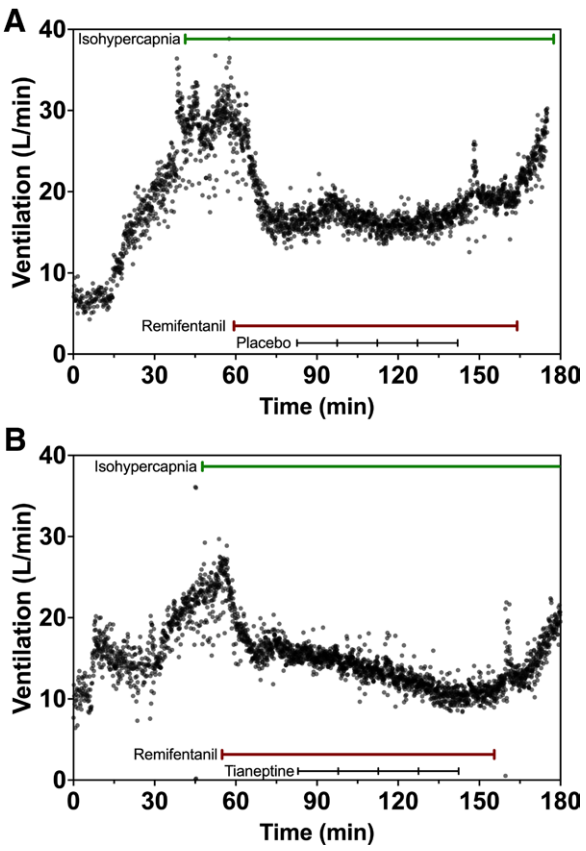

Fig. 4. Examples of the ventilatory effect of intravenous placebo (*A*) and tianeptine (*B*) on remifentanil-induced respiratory depression (study 2b). The *dots* show ventilation, with each dot representing one breath. The *red line* represents remifentanil infusion, the *black line* represents the four placebo or tianeptine steps, and the *green line* represents the isohypercapnic period. The data are from subject 001.

metabolite in urine.[11] Both tianeptine and MC5 possess antidepressant activity.[11] Tianeptine induces mood improvement and antianxiety effects by modification of synaptic plasticity and improving the performance of brain networks involved in mood and affective functioning.[8–10] Relevant to opioid-induced respiratory depression, tianeptine enhances AMPA receptor-mediated transmission by acting at allosteric sites; it increases AMPA receptor currents through kinase phosphorylation; and at the same time, glutamatergic transmission at *N*-methyl-D-aspartate receptors is reduced by tianeptine.[8–10] Both mechanisms may cause respiratory stimulation during opioid-induced respiratory depression. For example, the ampakines, that are able to counteract opioid-induced respiratory depression, do so by facilitating AMPA receptor-mediated glutamatergic transmission,[2,21] while ketamine, another drug, that is able to alleviate opioid-induced respiratory depression at subanesthetic doses, reduces *N*-methyl-D-aspartate–mediated

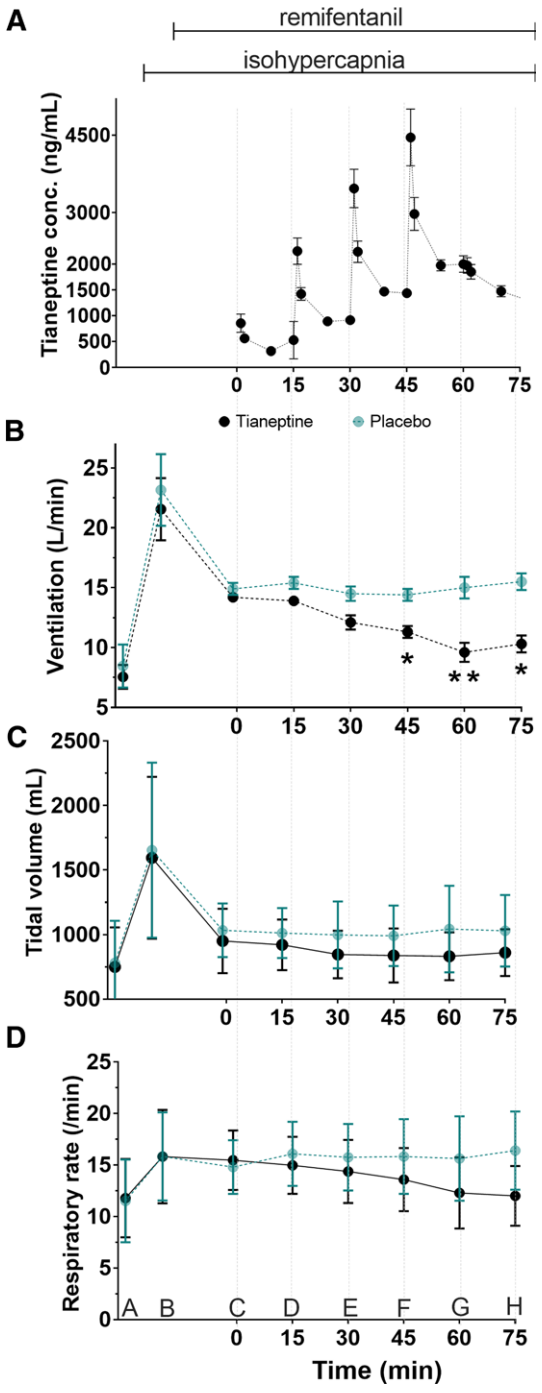

Fig. 5. Results of study 2b performed in 15 subjects. T = 0 min is the start of tianeptine (*green symbols*) or placebo (*black symbols*) infusion; T = 60 min is the end of tianeptine infusion. Timepoint *A* shows the baseline. Timepoint *B* shows isohypercapnia. Timepoints *C* to G show the 15-min intervals corresponding to tianeptine dose escalation. Timepoint *H* is 15 min following the end of tianeptine infusion. **P* < 0.001 *versus* placebo; ***P* = 0.001 *versus* placebo. The data are means ± SD. No statistical analysis was performed on tidal volume and respiratory rate. (*A*) Tianeptine concentration. (*B*) Ventilation. (*C*) Tidal volume. (*D*) Respiratory rate.

glutamatergic neurotransmission.[20] Hence, from a theoretical point of view, tianeptine is a valid candidate to counteract or prevent respiratory depression induced by opioids in ways similar to the ampakines and ketamine. Finally, tianeptine does act as an agonist on μ-opioid receptors, which may reduce its respiratory stimulatory capabilities.[12]

Animal Study

Cavalla *et al.*[7] studied the effect of tianeptine in conscious rats. The animals were pretreated with tianeptine 2 and 10 mg/kg, given intraperitoneally, 5 min before 10 mg/kg morphine, given intraperitoneally; $\dot{V}_E$ was measured by whole body plethysmography. Control arms consisted of pretreatment with placebo, the ampakine CX-546, and the tianeptine analog DP-201. Low-dose tianeptine, CX-546, and DP-201 but not high-dose tianeptine effectively increased respiratory activity before any morphine administration. In contrast to placebo, both tianeptine doses, CX-546, and DP-201 effectively prevented morphine-induced respiratory depression for at least 60 min after morphine injection. These results support the theoretical notion that tianeptine is a viable drug to be used in the treatment of opioid-induced respiratory depression.

Study 1

In the initial proof-of-concept trial, we tested the effect of pretreatment with oral tianeptine (37.5, 50, and 100 mg) and placebo on alfentanil-induced respiratory depression in healthy male and female volunteers. Our approach was similar to that of Oertel *et al.*,[21] who tested the effect of the ampakine CX717 on alfentanil-induced respiratory depression (alfentanil target concentration of 100 ng/ml) on the $\dot{V}_E55$ of the hypercapnic ventilatory response in 15 healthy volunteers and observed an increase in $\dot{V}_E55$ of 5.2 l/min from alfentanil/placebo to alfentanil/CX717 ($p = 0.02$). After the intake of 50 mg tianeptine, we observed that alfentanil $\dot{V}_E55$ was greater by 4.2 l/min compared to placebo ($P = 0.070$). We considered this the signal that we were searching for and subsequently initiated the development of an intravenous tianeptine formulation. Interestingly, no effect was observed when the tianeptine dose was increased to 100 mg and the alfentanil target concentration was lowered to 50 ng/ml. At the time, we related this to the small sample size ($n = 8$/group).

Study 2

After the development of intravenous tianeptine, we performed a pharmacokinetic study that allowed the design of the randomized controlled trial. The trial itself was modeled according to an earlier protocol that showed that intravenous *S*-ketamine partly restored remifentanil-induced respiratory depression.[20] The target remifentanil concentration, the magnitude of the remifentanil-induced respiratory depression, and the isohypercapnic levels were all comparable between the two studies. In contrast to expectation, we observed a slow decline in isohypercapnic $\dot{V}_E$ by approximately 5 l/min during the 1-h tianeptine infusion. These data are in sharp contrast to the animal study but also to study 1, which did not show a decrease in $\dot{V}_E55$ at any time period after tianeptine pretreatment. Several nonmutually exclusive mechanisms may be responsible for our findings. There are suggestions in the animal study, as well as in study 1, that tianeptine has a bell-shaped dose-response curve.[7] This then suggests that the excitatory effects of tianeptine on respiration wane at higher brain concentrations. This may well be related to the opioid receptor effects of tianeptine.[12,22,23] Gassaway *et al.*[12] showed that tianeptine is a full agonist at μ- and δ-opioid receptors, while Samuels *et al.*[23] showed opioid effects induced by tianeptine's metabolite MC5. It was speculated that these opioid effects could be responsible for triggering many of the effects attributed to tianeptine, including antidepression and anxiolysis.[12,22,23] Animal studies did find that tianeptine is an effective analgesic in acute and chronic inflammatory pain, related to μ-opioid receptor activation but also to activated adrenergic neurotransmission.[24,25] Finally, intoxication with tianeptine, often combined with other substances, is well treated with naloxone,[26,27] although there are case reports that describe acute and chronic high-dose tianeptine abuse (750 to 3,000 mg/day) without any cardiorespiratory side effects.[28,29] These latter observations suggest the absence of a clinically relevant opioid effect in humans. Given all of the above, we conclude that tianeptine over the concentration range of 500 to 2,000 ng/ml worsened the respiratory depression induced by remifentanil, possibly related to its μ-opioid agonistic effect, although we cannot exclude other causes. To determine the dose dependency of tianeptine's respiratory effects, it is necessary to study the effect of different doses on baseline ventilation and the hypercapnic ventilatory response without concomitant opioid infusion.

Another cause of the respiratory depression induced by tianeptine may be its sedative effects. In study 2b, when queried, all subjects indicated an increase in the level of sedation; however, we did not quantify this effect. Increase in sedation from any cause may worsen opioid-induced respiratory depression.[30] Our and other data indicate that sedatives such as alcohol, benzodiazepines, and also antidepressants worsen opioid-induced respiratory depression.[14,29] We considered some other issues that might have differed between the placebo and tianeptine arms of our randomized trial, such as differences in sensations that may have occurred during infusion of tianeptine *versus* placebo or unintentional differences in end-tidal CO_2 between study arms. Still, the study was fully blinded, and there were no differences in baseline $\dot{V}_E$, isohypercapnic level, and end-expired CO_2 control between study arms, and also no order effect was present in the data. In addition, none of the subjects complained of pain upon injection. Hence, there are

no methodologic issues or any imbalance between study arms that can explain the enhancement of remifentanil-induced respiratory depression in our study. Studies 1 and 2b, however, differed in the timing of treatment with tianeptine, pretreatment in study 1 (replicating the animal study of Cavalla et al.[7]), and tianeptine infusion after the establishment of respiratory depression in study 2. Still, it seems improbable that a fixed respiratory depressant effect precluded a clinical effect from tianeptine as a respiratory stimulant, since the animal data show that ampakines given before or after fentanyl both effectively reduce ventilatory depression.[31] Finally, we induced respiratory depression by two distinct phenylpiperidine derivatives with very different pharmacokinetics but similar pharmacodynamics. This was done to replicate earlier studies with these two opioids.[20,21] Whether the use of remifentanil contributed to the rejection of our hypothesis is questionable, as an earlier study showed that its respiratory effects are successfully counteracted by low-dose ketamine.[20]

Future Perspectives

We recently reviewed all current nonnaloxone reversal strategies currently applied or under development.[6] These included partial opioid agonists, cannabinoid 2 receptor agonists, ketamine, thyrotropin-releasing hormone, oxytocin, nicotinic acetylcholine receptor agonists, ampakines, serotonin receptor agonists, antioxidants, background potassium channel blockers, and opioid sequestration techniques. We argued that currently none of these often-still-experimental therapies are sufficiently examined with respect to effect and safety, and many of the compounds have little effect at deeper levels of respiratory depression or come with many side effects.[6] We therefore suggest development of reversal strategies that combine respiratory stimulants with, for example, naloxone. Possibly low-dose tianeptine combined with low-dose naloxone will attenuate any clinically relevant opioid effect, and consequently this combination will be able to effectively counteract opioid-induced respiratory depression.

Finally, we argue that our stepwise approach, *i.e.*, review of pharmacologic and animal data followed by a proof-of-concept study and finally a phase 1 randomized controlled trial (both studies were performed in established models of respiratory depression in human volunteers), exemplifies how we envision that nonopioid respiratory stimulants should be tested. Our project therefore serves as a model for studies that attempt to develop reversal strategies for potent opioid-related respiratory toxicity.

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Competing Interests

Drs. McMorn, Snape, Horrigan, Evans, and Kiernan are employees of AMO Pharma Ltd. (Leeds, United Kingdom) and are shareholders of the company. Dr. Cavalla is employee of Numedicus Ltd. (Cambridge, United Kingdom). Dr. Dahan received consultancy and/or speaker fees from Enalare Therapeutics Inc. (Naples, Florida), Grünenthal BV (Breukelen, The Netherlands), Medasense Biometrics Ltd. (Tel Aviv, Israel), Trevena Inc. (Chesterbrook, Pennsylvania), and MSD Nederland BV (Haarlem, The Netherlands). The Anesthesia and Pain Research Unit of the Department of Anesthesiology, Leiden University Medical Center (Leiden, The Netherlands) received/receives funding from AMO Pharma Ltd., Bedrocan BV (Emmeloord, The Netherlands), Grünenthal GmbH (Stolberg, Germany), Medasense Biometrics Ltd. (Tel Aviv, Israel), Medtronic (Washington, D.C.), MSD Nederland BV (Haarlem, The Netherlands), LTS Lohmann Therapie Systeme AG (Andernach, Germany), and Trevena Inc. (Chesterbrook, Pennsylvania). The other authors declare no competing interests.

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The Leech Airway: A Flute for Your "Champagne"?

In 1937, Canadian anesthesiologist Beverley Leech, M.D. (1898 to 1960), patented an early precursor to the laryngeal mask airway (LMA, *lower left*). His "pharyngeal bulb gasway," also called the Leech airway, featured a soft, detachable rubber bulb around a tough metal core (*upper left*). Leech's love for cyclopropane (*right*), dubbed the "champagne" of volatile anesthetics, inspired the airway's design. Although rapid and smooth in onset, cyclopropane was expensive and explosive, mandating closed-circuit delivery. However, leak-free ventilation was challenging to achieve, as endotracheal intubation had yet to become routine. Laryngoscopes and tubes were still being refined, and prolonged laryngospasm easily occurred pre-curare. To avoid the risk of intubation, Leech envisioned a supraglottic airway that would optimize cyclopropane delivery through a closed circuit. For more than a year, he painstakingly examined the wax casts of cadaver throats to design a malleable bulb that conformed to the average adult pharynx. Once manufactured, the Leech airway gained favor. Its bulb, lubricated with Vaseline, could be advanced gently into the oropharynx of a mask-induced patient. However, when succinylcholine arrived in 1952, wondrously facilitating tracheal intubation, the Leech airway became obsolete. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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