Is opiate action in cough due to sedation?

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Abstract

Objectives: Opiates have been used for cough suppression for centuries. It is unclear whether this antitussive action is due to their known sedative effects. We aimed to assess correlation between cough suppression and opiate usage.

Methods: We performed a post hoc analysis of two published trials with three opioids. In study one, patients with chronic cough were treated with 4 weeks of modified release morphine sulphate (5 mg twice daily) or placebo in a double-blinded placebo-controlled fashion. Cough suppression was assessed subjectively by the Leicester Cough Questionnaire and objectively by citric acid aerosol (CAA) induced cough challenge. In study 2, normal volunteers were given single doses of placebo, codeine 30 mg or dextromethorphan 50 mg and cough suppression assessed using the CAA-induced cough challenge. Sedation was contemporaneously assessed by direct questioning.

Results: There were 14 episodes of patient-reported sedation; 2 with modified release morphine sulphate, 9 with codeine and 3 with dextromethorphan. There was no correlation between change in the Leicester Cough Questionnaire or the CAA-induced cough challenge and reported sedation.

Conclusion: This observational study suggests that sedation is unlikely to underlie the antitussive properties of these opioids. Eliciting the mechanism of these medications in cough may be a target for future tailored drug development.

Keywords: antitussive, codeine phosphate, cough therapies dextromethorphan, morphine sulphate (MST), sedation

Introduction

Chronic cough is a common problem which can have a significant negative impact on patient quality of life [French *et al.* 1998]. In a UK based primary care survey, 12% of subjects had a chronic cough with 7% feeling that it significantly impacted on their lives [Ford *et al.* 2006]. Acute cough sufferers regularly seek medical advice and purchase over-the-counter medications for cough relief at an estimated cost of £104 million per year [Morice *et al.* 2006] in the UK.

Opiates have had a long history of use as antitussives. Dextromethorphan (DEX), a synthetic opioid, is the most widely used over-the-counter cough suppressant which has been shown to be effective both in the clinical setting and in experimental cough challenge studies in normal volunteers [Mathys, 1983; Parvez *et al.* 1996]. Historically, codeine preparations have been widely used though their clinical efficacy is less certain [Mudge, 1778].

In chronic cough, opiates are recommended for cough suppression though there are major concerns with their use [Chung, 2005]. We have shown that low dose modified release morphine sulphate (MST, 5 mg twice daily) was associated with a significant reduction in subjective cough counts and improvement quality of life for patients with chronic cough [Morice *et al.* 2007].

The opiate mechanism of cough suppression is poorly understood. Opiates have been used as a cough remedy since the 18th century [Sanders, 2007]. One of the possible mechanisms could be through a sedative action. It is well recognized that opiates have sedative side effects [Forrest *et al.*, 1977; Bruera *et al.* 1989]. Hydrocodone, alfentanil and fentanyl have been assessed as alternative sedative agents in fiberoptic bronchoscopy [Webb *et al.* 1989; Papagiannis and Smith 1994; Stolz *et al.* 2004] with subjective observer cough reduction as a secondary outcome.

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Here we performed a post hoc analysis of two separate studies investigating the antitussive effects of opiates to determine if there is a relationship between the degree of cough suppression and drowsiness. Efficacy analyses of the individual studies have been previously published [Morice *et al.* 2007; Morjaria *et al.* 2013].

Methods

Study 1: Modified release MST versus placebo in patients with chronic cough [Morice et al. 2007]

Patients with chronic cough (defined as >3 months duration) who failed to improve with specifically targeted antitussive therapy were recruited from our tertiary cough clinic at Castle Hill Hospital, Cottingham, UK. Patients were randomized into a double-blind placebo-controlled crossover study of 4 weeks MST 5 mg twice daily *versus* matched placebo. Cough was assessed using the Leicester Cough Questionnaire (LCQ), daily symptom diary and citric acid aerosol (CAA) cough challenge. Sedation was assessed at each visit as part of a binary symptom checklist.

Study 2: DEX and codeine versus placebo in normal volunteers [Morjaria et al. 2013]

Healthy volunteers aged 18–65 years were recruited to attend the clinical trials unit, Castle Hill Hospital, Cottingham, UK. Volunteers were required to have a reproducible cough challenge on 2 separate visits at least 5 days apart using the validated CAA-induced cough challenge model [Morice *et al.* 2001].

At subsequent visits the subjects were randomized in a double-blinded, placebo-controlled, crossover fashion to receive placebo, DEX 50 mg or codeine 60 mg. Antitussive activity was assessed at 15 min, 1, 2, 4 and 6 hours after administration of the study substance. Sedation was assessed contemporaneously by verbal adverse event reporting and recorded in the clinical record form.

Consent and ethics

All subjects gave informed written consent to participation in the studies and ethics approval was sought from the Hull and East Riding Local Research and Ethics Committee (Study 1: ISRCTN 18474014; Study 2: CRSN 2000103).

Data analyses

Subject baseline demographics were expressed as mean ($\pm$ SD) or median (IQR) depending on whether they were parametric or nonparametric respectively. These were obtained using Statistical Package for Social Science (SPSS for Windows version 18.0, Chicago, USA). The 6-hour area under the curve (AUC_{6hrs}) of change in cough for each individual patient was calculated using the trapezoidal rule. The comparison of sedation *versus* antitussive activity is displayed graphically in Figures 1 and 2.

Results

Demographic data of both studies are shown in Table 1.

Study 1

A total of 27 subjects (18 female) completed the study with a mean age of 55 (± 10.6) years. Overall the study showed an improvement in the LCQ with MST treatment (12.3 ± 2.5 at baseline increasing to 15.5 ± 2.7 on MST, $p < 0.01$) and a trend to improvement in CAA-induced cough challenge, though this did not reach significance. The two patients reporting drowsiness with MST are identified in Figures 1 and 2.

Study 2

A total of 50 subjects (30 female) were enrolled with 41 completing the protocol. Their mean age was 32.1 (± 11.2) years. Whilst there was no observed difference in overall cough suppression as assessed by the CAA-induced cough challenge model between codeine and DEX monotherapy, the difference was significant with combination therapy. The individual degree of cough suppression as evidenced by change in cough AUC_{6hrs} is shown in Figure 2. The nine patients who reported drowsiness with codeine and three with DEX are highlighted in Figure 2. There was clearly no association between cough reduction and sedation.

Discussion

Patients with chronic refractory cough suffer from a decrement in quality of life similar to patients with severe chronic obstructive pulmonary disease [French *et al.* 1998]. Therapeutic options are limited and there is a pressing need to develop novel treatments. In this retrospective post hoc analysis of two separate studies of opioids in

Figure 1. Modified release morphine sulphate (MST) 5 mg twice daily in patients with chronic cough. Cough challenge data set = change in C2 citric acid aerosol (CAA) cough challenge in the 6-hour area under the curve (AUC_{6hrs}) from baseline to post 4 weeks MST. QoL dataset = change in quality of life (QoL) as assessed by Leicester Cough Questionnaire (LCQ) at baseline and post 4 weeks MST. Higher LCQ indicates better quality of life. Red and green lines indicate the same 2 patients reporting sedation with their CAA cough challenge and LCQ.

Figure 2. Citric acid aerosol (CAA) cough challenge. Modified release morphine sulphate (MST) 5 mg twice daily for chronic cough = change in C2 CAA cough challenge from baseline to post 4 weeks MST. Codeine 60 mg single dose and dextromethorphan (Dex) 50 mg single dose data in normal volunteers = change in the 6-hour area under the curve (AUC_{6hrs}) from baseline post medication. High logC2 values imply higher cough threshold. Red lines indicate subjects reporting sedation (MST $n = 2$, codeine $n = 9$, DEX $n = 3$).

cough we have examined the link between reported reductions in subjective and objective indices of cough severity and sedation, and found there to be no apparent relationship.

Sedation during anaesthesia has a variable effect on cough reflex sensitivity dependent on the anaesthetic agent used and the level of anaesthesia achieved. Only with profound sedation, when

depression of the medullary centres is sufficient to cause apnoea, does abolition of the cough reflex occur [Eccles, 2009]. When cough has been assessed in sleep, both animal and human studies have shown a decrease in coughing episodes [Decalmer *et al.* 2007] and a change in cough threshold [Sullivan *et al.* 1978, 1979]. Patients comatose due to head injury continue to demonstrate a cough reflex [Eccles, 2009].

Table 1. Demographic data for each study.

		Study 1: low dose modified release MST	Study 2: codeine or DEX
Study group		Patients with chronic cough	Normal volunteers
Total subjects		27	50
Age		55 ($\pm$ 10.6)	32.06 ($\pm$ 11.15)
Gender	Male	9	20
	Female	18	30
Smokers		0	0
LCQ improvement		3.2	-
DEX, dextromethorphan; LCQ, Leicester Cough Questionnaire; MST, morphine sulphate.			

Studies over the past few decades have failed to clarify the neurophysiology of the cough reflex [Canning, 2006]. There is a suggestion that vagal afferent nerve subtypes other than rapidly adapting receptors (RARs) and C-fibres as well as other somatosensory visceral innervations may be involved. Our analysis shows that those subjects who have the greatest efficacy in terms of cough suppression were not those who reported significant sedation. If sedation was the main antitussive mechanism of these agents, then those reporting sedation would be also those with the greatest antitussive response. There were only 2 subjects who reported sedation in the MST study (7.4%), but 9 patients in the codeine study (30%). This suggests a large difference in the plasma concentrations of morphine between the two studies with some individuals in the codeine study having substantially higher levels of the active opiate. The variable population pharmacokinetics of codeine are due to the polymorphic expression of the P450 2D6 enzyme which converts codeine to its active metabolites; however, MST has a more consistent bioavailability resulting in more predictable levels of the presumed active morphine glucuronides. Akin to morphine, DEX, a D-isomer of morphine with reputedly fewer side effects, caused sedation in three subjects which was unrelated to antitussive efficacy.

This lack of association between sedation and antitussive activity is apparent in both objective (CAA-induced cough challenge) and subjective (LCQ) assessments of cough. Ideally, these various modalities of assessment should be combined to form a composite of response since each modality assesses a different facet of cough [Morjaria *et al.* 2013]. In the first study, there was significant improvements in subjective cough assessment but this was not replicated objectively undermining the importance of the CAA-induced

cough challenge model in the assessment of cough [Doherty *et al.* 2000; Ramsay *et al.* 2008]. Sedation was assessed *via* prompted patient self reporting rather than specific metrics since these have only been applied to patients in the intensive care setting [Ramsay *et al.* 1974; Sessler *et al.* 2002]. Other opiate specific scales such as the Pasero Opioid-Induced Sedation [Pasero, 2009] scale are similarly inappropriate since they are validated for postoperative pain management.

There are some cautions in the interpretation of our study which need clarification. Firstly, this is a post hoc analysis of two studies not specifically designed to assess the sedative effects of opiates. Although the data were prospectively recorded and clearly demonstrated that there is no concordance between parameters of cough suppression and subjective reporting of sedation, further studies powered for a primary endpoint of sedation would be required for rigorous proof. Secondly, whilst these observations used the subjective reports of sedation contemporaneously obtained at clinic visits, daily assessment may be preferable using a metric scale. Additionally, our studies were not set up to assess the endpoints associated with long-term use of opiates in clinical practice.

In conclusion, we have found no relationship between the sedative action of the three different opioids and various measures of their antitussive activity. Whilst sedation has undoubted effects on cough reflex sensitivity, the opiate pathways targeted by pharmacological agents clearly have alternative loci of activity. This segregation of effects suggests that future drug development may be able to specifically target antitussive activity.

Conflict of interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.

pdf (available on request from the corresponding author). R.S.D. and C.E.W. have no declarations. J.B.M. has received honoraria for speaking and financial support to attend meetings/advisory boards from Chiesi, Pfizer, MSD, Boehringer Ingelheim, GSK/Allen & Hanbury, Teva, Napp and Novartis. A.H.M. has received honoraria for speaker meetings and financial support to attend meetings/advisory boards from Chiesi, Pfizer, MSD, Boehringer Ingelheim, Novartis, GSK, AstraZeneca, Proctor & Gamble Healthcare, Orion Respiratory UK, Vectura Ltd and Nycomed.

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