Tussive effect of a fentanyl bolus

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The aim of this study was to investigate the incidence of pre-induction coughing, after an iv bolus of fentanyl. The study sample was 250 ASA physical status I–II patients, scheduled for various elective surgical procedures. The first 100 were randomly allocated to recieve 1.5 $\mu g \cdot kg^{-1}$ fentanyl via a peripheral venous cannula (Group 1), or an equivalent volume of saline (Group 2). Twenty-eight per cent of patients who received fentanyl, but none given saline, coughed within one minute ($P < 0.0001$). The second 150 patients were then randomly assigned to three equal pretreatment groups. Group 3 received 0.01 $mg \cdot kg^{-1}$ atropine iv one minute before fentanyl. Groups 4 and 5 received 0.2 $mg \cdot kg^{-1}$ morphine im, and 7.5 mg midazolam po, respectively, one hour before fentanyl. Thirty per cent of patients in Group 3, 6% in Group 4, and 40% in Group 5, had a cough response to fentanyl. Fentanyl, when given through a peripheral cannula, provoked cough in a considerable proportion of patients. This was not altered by premedication with atropine or midazolam, but was reduced after morphine ($P < 0.01$). Coughing upon induction of anaesthesia is undesirable in some patients, and stimulation of cough by fentanyl in unpremedicated patients may be of clinical importance.

Le but de cette étude était d'investiguer l'incidence de la toux pré-induction après bolus intraveineux de fentanyl. La population de l'étude était de 250 patients ASA I–II cédulés pour des procédures chirurgicales électives variées. Les premiers 100 patients furent randomisés afin de recevoir 1.5 $\mu g \cdot kg^{-1}$ de fentanyl à travers une canule veineuse périphérique (Groupe 1), ou un volume équivalent de salin (Groupe 2). Vingt-huit pour cent des patients y ont reçu du fentanyl mais aucun de ceux qui ont reçu du salin, ont toussé à l'intérieur d'une minute ($P < 0,0001$). Les 150 autres patients furent ensuite randomisés en trois groupes égaux de prétraitement. Le groupe 3 a reçu 0,01 $mg \cdot kg^{-1}$ d'atropine iv une minute avant le fentanyl et le groupe 4 et 5 ont reçu 0,2 $mg \cdot kg^{-1}$ de morphine im et 7,5 mg de midazolam po, respectivement, une heure avant le fentanyl. Trente pour cent des patients dans le Groupe 3, 6% dans le Groupe 4, et 40% dans le Groupe 5, ont présenté de la toux lors de l'injéction du fentanyl. Le fentanyl, lorsqu'administré dans une canule périphérique, a provoqué de la toux chez un grand nombre de patients. Ceci ne fut pas altéré par la prémédication avec l'atropine ou le midazolam mais fut réduit après morphine ($P < 0,01$). La toux lors de l'induction de l'anesthésie n'est pas désirée chez certains patients, et la stimulation de la toux par le fentanyl chez des patients non-prémédiqués peut être d'une importance clinique.

Key words
ANALGESICS: fentanyl;
COUGH.

One of the useful side-effects of opioid analgesics is suppression of the cough reflex,[1] and is the basis of their use in oral cough suppresants.[2] However, we have observed that some patients coughed after an iv bolus of fentanyl. This relatively unknown effect of fentanyl has only recently been reported in the anaesthetic literature.[3] A double-blind, prospective, randomized controlled trial was conducted to establish the incidence of coughing, after a peripheral iv bolus of fentanyl, and the modulation of this effect with vagolytic, hypnotic and narcotic premedication.

Methods
The trial protocol was approved by our hospital's Medical Research and Ethics Committee.

This study was conducted in two parts. In the first, 100 ASA physical status I–II patients, for various surgical procedures, were randomly assigned into a trial (Group 1) and a control group (Group 2). In part two, another 150 ASA physical status I–II patients were randomly assigned into three equal pretreatment groups. Randomization was done by a random number generator, a software within the Epistat program. Exclusion criteria included history of asthma,[4] chronic non-productive cough,[5] upper respiratory tract infection[6] in the last two weeks, or smoking. Patients on angiotensin converting enzyme inhibitors were also excluded.[7] All had normal intracranial pressure[8] and intact globes.[9] None was scheduled for head or neck surgery.[10] They recieved no premedication, other than those for pre-existing, non-respiratory diseases.

The groups were treated as follows:

Group 1 received 1.5 $\mu g \cdot kg^{-1}$ of preservative-free fentanyl, at room temperature, as a bolus, in a peripheral running *iv* infusion of dextrose in saline.

Group 2 received an equivalent volume of room temperature saline.

Group 3 received 0.01 $mg \cdot kg^{-1}$ atropine *iv*, one minute before the fentanyl.

Group 4 received 0.2 $mg \cdot kg^{-1}$ morphine *im*, one hour before the fentanyl.

Group 5 received 7.5 mg midazolam *po*, one hour before the fentanyl.

Heart rate (HR) and oxygen saturation (SaO_2) were continuously monitored. Blood pressure was measured before and one minute after administration of the test solution. The patients were observed for one minute for any cough, defined as "a sudden noisy expulsion of air from the lungs, usually produced to keep the airways of the lungs free of foreign matter."[11]

For Groups 1 and 2, the operator administering the *iv* solution was given an unmarked syringe containing either fentanyl or saline, prepared by a second operator. For Groups 3, 4 and 5, the operator was not aware of the type of pretreatment. The patients though aware of the type of premedication, were not aware of the nature of the trial. Informed consent was not sought as the trial was not expected to pose any risk, and knowledge of the trial might bias the patients.

Analysis of variance (ANOVA) was applied to compare the age and weight among the five groups. Fisher's exact test [FET] was applied to compare the results among groups.

Results

There were no significant changes in SaO_2 or haemodynamic variables, except in the atropine pretreatment group, where HR increased $29.3 \pm 17.5\%$. The five groups were comparable for age and body weight (Table I). None of the 50 control patients coughed after the bolus of saline. The number that coughed within one minute of *iv* fentanyl were 14 (28%) of the patients in Group 1, 15 (30%) in Group 3, three (6%) in Group 4 and 20 (40%) in Group 5 (Table II).

TABLE I   Demographic data of patients

Group	Age (yr)	Weight (kg)
1	30.9 ± 9.9	56.3 ± 10.7
2	33.4 ± 8.8	57.4 ± 9.9
3	31.5 ± 9.8	54.5 ± 9.9
4	34.9 ± 10.9	56.7 ± 9.4
5	34.5 ± 8.6	55.2 ± 8.5

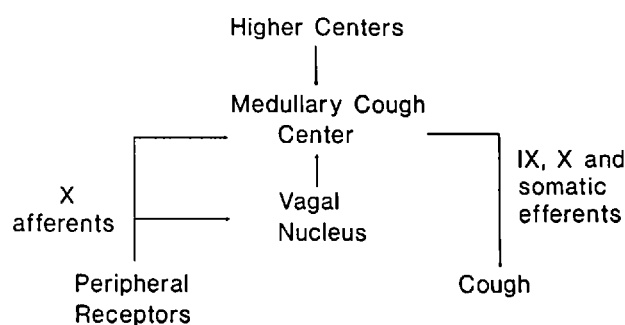Values are expressed as mean ± SD.

COUGH REFLEX ARC

FIGURE   Cough reflex arc.

Comparing Groups 1 and 2, fentanyl provoked cough in a significant proportion of patients at $P < 0.0001$. Comparing each pretreatment group against Group 1, the P values were not significant for Groups 3 and 5. For Group 4 the P value was significant at $P < 0.01$.

Discussion

Fentanyl, via a peripheral venous line, provoked cough in 28% of patients. This decreased after pretreatment with morphine, but not after vagolytic or midazolam premedication.

This contrasts with Bohrer's series[3] where only 2.7% of patients given 7 $\mu g \cdot kg^{-1}$ fentanyl via a peripheral cannula had a cough response, while 45.9% coughed after a bolus of 7 $\mu g \cdot kg^{-1}$ through a central venous line. In that trial the patients were premedicated with 0.1 $mg \cdot kg^{-1}$ midazolam *im*. In our 7.5 mg oral midazolam pretreatment group, the incidence of cough response was 40%. The difference may be due to a dose-specific effect of fentanyl at effector sites. It could also be affected by the different routes of midazolam premedication or differences in the rate of injection of fentanyl.

The Figure is a simplified circuit of the cough reflex arc. The medullary cough centre receives afferent signals via the vagus. It also receives contributions from the vagal nucleus and higher brain stem and cortical centers.

TABLE II   Results of trial

Group	Number of patients that coughed (%)	Total (%)
1	14 (28)	50 (100)
2	0	50 (100)
3	15 (30)	50 (100)
4	3 (6)	50 (100)
5	20 (40)	50 (100)

TABLE III   Possible pathways for FCR

Peripheral factors

Stimulus	Receptor	Afferent pathway	Effect
Pulmonary congestion Lobeline sulphate Enkephalin analog	J Receptors	Vagal C	dyspnoea dyspnoea + cough ? cough
Deep inspiration	Stretch receptors	Vagal	Cough
Mechanical (+ tracheal and broncho-constriction) Chemical (histamine)	Irritant receptors at trachea and bronchi at lower levels	Vagal	cough shallow breathing + broncho-constriction

Central factors

Stimulus	Receptor	Efferent pathway	Effect
Opiates	Vagal nucleus	Vagal	broncho-constriction and histamine release
	Caudate nucleus	Striatal nigral	muscle rigidity
	Medullary opiate receptor ? tussive receptor	? Vagal	cough suppression ? cough ? biphasic, stimulation followed by suppression

Outflow is via vagal, glossopharyngeal and somatic efferents to effect cough. For this discussion we shall term the cough provoked by fentanyl a fentanyl cough reflex (FCR). Fentanyl may provoke cough by stimulating peripheral receptors, or it may act through central receptors or pathways. The possible pathways for FCR are shown in Table III.

The natural stimulus for J receptors is pulmonary congestion, perceived as dyspnoea[12] and can be blocked by vagotomy.[13] In man the response of these receptors to lobeline sulphate is cough.[14] Sapru[15] found that these could be stimulated by an enkephalin-analog. Bohrer[3] suggested that FCR arose as a result of J receptor stimulation. Atropine, a vagolytic at muscuranic sites, did not decrease FCR, despite producing significant tachycardia. This suggests that vagal efferent pathways, acting via muscuranic receptors, may not be involved in FCR. It would be interesting to study the effects of a bolus of fentanyl in patients with vagal block, as in Guz et al.'s patients,[13] or in patients who have received lung transplants.

Stretch receptors can trigger cough and bronchoconstriction upon deep inspiration, especially in asthmatics. This presumably requires inflammatory "priming" of the rapidly adapting irritant receptors.[16] This is an unlikely mechanism of FCR since patients with reactive airway or inflammatory disease were excluded, and there was no airway or ventilatory manoeuvres.

Irritant receptors in the upper pulmonary mucosa are more sensitive to mechanical stimuli, while those at the lower level are triggered by chemical stimuli.[12] In man, stimulation of these deeper receptors causes rapid shallow breathing and bronchoconstriction. Stimulation of the upper pulmonary receptors causes cough. Irritant receptors can also be stimulated by deformation of the mucosa, secondary to tracheal smooth muscle constriction[17] or bronchoconstriction.[18] As fentanyl has been reported to contract tracheal smooth muscle,[19] these receptors are possible afferent sites for FCR.

Bronchomotor tone is augmented by central vagal discharge,[20] and fentanyl is known to stimulate the vagal nucleus.[21] Histamine can also stimulate irritant receptors, either directly[22] or via triggering bronchoconstriction.[18] Fentanyl does not cause direct release of histamine,[23] but preganglionic parasympathetic stimulation has been shown to augment histamine release by mast cells.[24] Vagotomy attenuated the effects of central vagal stimulation by fentanyl.[21] Thus vagally mediated bronchoconstriction or histamine release is an unlikely mechanism for FCR, as incidence of cough was not affected by atropine premedication.

Sudden adduction of the vocal cords or supraglottic obstruction by soft tissues, secondary to muscle rigidity,[25] may trigger a cough. The mechanism is by activation of Mu receptors on interneurons in the caudate nucleus, with enhanced central striatal dopamine de-

gradation.[26] GABA receptor agonists and antagonists have also been applied to the substantia nigra with modulation of this narcotic-induced rigidity.[27] Benzodiazepines have GABA receptor agonistic properties,[28] which could modify the response of striatal-nigral pathways to a bolus of fentanyl. However, midazolam premedication did not significantly alter our incidence of FCR.

Opioids depress the cough reflex, by a direct effect on the medullary cough centre. This involves opiate receptors that are less stereospecific, and less sensitive to naloxone, than those responsible for analgesia. With several opioids, the dose required to supress cough is lower than that required for analgesia.[1] Also, the degree of relief reported by patients, given codeine, does not correlate with the actual reduction of frequency of coughing.[2] All this supports receptor dualism, with distinct receptors mediating the antitussive action of opioids, as opposed to those for analgesia.

In both Bohrer's[3] and our studies, fentanyl was given rapidly. "Slug" pharmacokinetics will affect drug delivery, favouring well-perfused organs with high lipid content. This may deliver different concentrations of molecules to different populations of opiate receptors.

Knoll,[29] found that an azidomorphine derivative stimulated some opiate receptors while inhibiting others. It is postulated here that selective distribution or dose of fentanyl may perhaps temporarily inhibit those receptors which are responsible for the antitussive property of opioids, while stimulating another unknown population of receptors, provoking FCR.

Conclusion

Fentanyl, when given through a peripheral cannula, provoked a cough response in a significant proportion of patients. This was not altered by premedication with atropine or midazolam. Opiate receptor dualism may be the factor mediating cough, or fentanyl may have a biphasic effect on opiate receptors, probably related to a specific dose range, governed by the rate of administration. Two other possible pathways for FCR, as discussed, involve stimulation of the J receptors or irritant receptors. The former would require relay of efferent signals independent of vagal efferent pathways acting via muscuranic receptors. The latter would be an indirect effect secondary to contraction of tracheal smooth muscle.

Coughing upon induction of anaesthesia is undesirable in patients with raised ICP or an open globe. Fentanyl at induction should be used with caution, even at doses of 1.5 $\mu g \cdot kg^{-1}$. In these and in patients with history of reactive airways, iv fentanyl at induction of anaesthesia should perhaps be preceded by opioid premedication.

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