Ann. Rev. Pharmacol. Toxicol. 1985. 25:41–65

THE EFFECT OF DRUGS ON RESPIRATION IN MAN

Arthur S. Keats

Division of Cardiovascular Anesthesia, Texas Heart Institute, and Department of Anesthesiology, University of Texas School of Medicine, Houston, Texas 77030

INTRODUCTION

Both previous reviewers (1, 2) of the subject of the effect of drugs on respiration in man noted that respiration may be markedly affected by drugs acting at sites other than the respiratory control center in the brain. Drugs may modify afferent input and transmission to the center or alter the mechanical properties and performance of the effector organ through its airways, circulation, or respiratory muscles. The effects of drugs such as the inhalation anesthetics on respiration are the result of actions on whole body and organ metabolism, on chemoreceptor sensitivity, on mechanical properties of the chest wall and bronchial tree, on volume and distribution of pulmonary blood flow, as well as on the respiratory control center. Of necessity, this review is limited to drugs whose predominant effect is by a mechanism involved in central respiratory control. Its emphasis is on the results of drug administrations rather than on the mechanisms that effect the changes. Because of the ease with which many aspects of respiration are now studied and the abundance of such studies, the data reviewed are limited to those obtained in man except where specifically stated. Further, all data cited were obtained from healthy subjects unless stipulated otherwise. Data reviewed here largely supplement other recent reviews applying to the broad title (3–5).

METHODS OF MEASUREMENT AND THEIR LIMITATIONS

Ideally, the measurement of drug effects on respiration should examine all mechanisms potentially affecting respiration, quantify each, and evolve an

0362-1642/85/0415-0041$02.00

integrated picture describing the contribution of each to the net effect observed following a therapeutic dose. The effect of morphine in man, for example, could be described in terms of proportionate changes in CO_2 production, chemoreceptor activity, central chemical sensitivity, altered airway resistance, and pulmonary ventilation/perfusion relationships that follow from a modified pattern of breathing. Such a description has not been attained for any drug. In terms of clinical usefulness and drug safety, the primary questions are: Does the drug act on respiratory control mechanisms leading to hypoventilation (respiratory depression) or hyperventilation (respiratory stimulation)? Is this effect greater or less than some reference drug? Is the effect dose related? To answer these questions, studies have been directed primarily to the measurement of changes in ventilation stimulated by high carbon dioxide or low oxygen in healthy subjects. The stimulus to respiration is expressed in terms of tension, PCO_2 or PO_2. Tensions are usually measured in end tidal gas samples, at times called alveolar gas samples, $P_{ET}CO_2$ or P_ACO_2. Less commonly they are determined from arterial blood ($PaCO_2$). These abbreviations will be used in subsequent descriptions.

The study of drug effects on some aspects of resting ventilation is seriously limited by the relatively small potential range of observed responses. Changes in gas exchange measured as respiratory rate, tidal or minute volume, or their consequence measured as $P_{ET}CO_2$, $PaCO_2$, or PaO_2, are small following doses of drugs that have a profound effect on stimulated respiration. For example, narcotic analgesics or inhalation anesthetics that increase resting $PaCO_2$ only 5 mmHg induce very large changes in the CO_2 response curve. The small range of potential responses decreases sensitivity for quantitative comparisons between drugs and a description of dose-response relationships. By contrast, the range of responses is greatly exaggerated when respiration is stressed by inspiration of high CO_2 or low O_2 tensions.

Response to Carbon-Dioxide Stimulation (CO_2 Response)

In normal subjects, increasing inspired PCO_2 dramatically increases minute volume of ventilation in an almost linear fashion, achieving expired volumes greater than 30 liters per minute at $P_{ET}CO_2$ less than 50 mmHg. Since hypoxia also increases the CO_2 response, 50% or more oxygen is used as the diluent gas to eliminate the chemoreceptor contribution to stimulation. The response to PCO_2 is exquisitely sensitive to drugs acting directly on the respiratory control center, and they alter this response by displacing the curve to the right and by decreasing its slope. No single expression quantifies these two changes. Potent analgesics in therapeutic doses displace curves to the right with small changes in slope, and the change can be quantified by measuring displacements in mmHg P_ACO_2 assuming parallel slopes. High doses of potent analgesics, especially if associated with marked sedation or sleep, as well as inhalation

anesthetics exert their predominant effect by decreasing slope, which is usually quantified as percent change from control. It is not unlikely that drugs that displace without changing slope and others that do the converse act at different sites within the intimate structure of the respiratory center. The practical problem is illustrated in Figure 1, which shows the effect of morphine in low dose to be displacement and in high dose to be a decrease in slope. Assumption of parallel slopes for the high dose curves will only measure displacement of the mean of the calculated curve. On the other hand, using change in slope as the measure, the effect of morphine 20 mg is small. At the moment there is no convention for measuring or reporting these changes, permitting easy comparison of drugs, or the construction of dose-effect curves.

A further difficulty in quantifying drug effects on the CO_2 response is that the method influences the curve obtained, leading to uncertainties in comparing results obtained by the two methods. In the rebreathing technique, during which the subject rebreathes from a bag containing oxygen and 6%–7% CO_2, the progressive increase in inspired CO_2 derives from endogenous CO_2 production and excretion into the bag. In this instance, the CO_2 gradient is from the tissues to the lung, and the PCO_2 stimulus in the respiratory center is higher than that measured as $P_{ET}CO_2$. Slopes of curves obtained in this way tend to be greater and displacement less than with curves obtained by breathing discrete CO_2 mixtures to steady-state ventilation without rebreathing. In the latter technique, the CO_2 gradient is from the lungs to the brain. A lower volume ventilation is then measured at a higher $P_{ET}CO_2$, with a decrease in slope of the CO_2 response curve. These differences were well illustrated in a detailed comparison of the two techniques in dogs (6). Problems in quantification of these curves and discussion of techniques and errors have been treated in detail by others (7–12).

CO_2 Stimulation at Constant PCO_2

A sensitive but seldom used method of quantifying drug effects on the CO_2 response is the continuous measurement of minute ventilation at a constant elevated end-tidal PCO_2. The method was first used by Lambertsen (13) to describe the time course of respiratory depression by intramuscular meperidine. He employed a continuous but varied inflow of CO_2 into the inspiratory limb of a non-rebreathing circuit to maintain constant end tidal PCO_2. The method measures continuously one point on the CO_2 response curve and ignores change in slope. It is ideally suited for determining the onset, peak, and duration of drug effect, particularly with drugs whose profile includes rapid onset and peak or short duration. Even the rebreathing method requires so much time that true onset and peak may be missed. A modification of this technique incorporates periodic determinations of the entire CO_2 response curve at intervals during continuous elevated PCO_2 breathing (14). A further modifica-

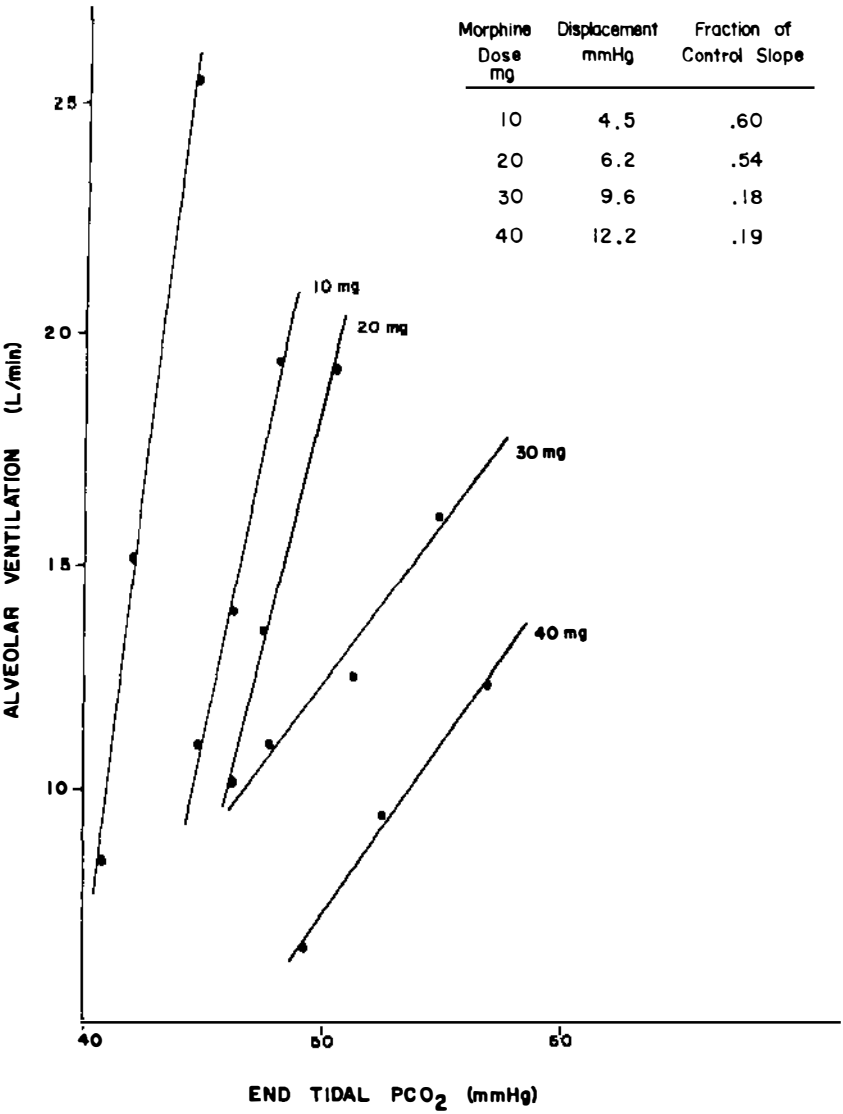

Figure 1 CO_2 response curves by the steady-state method from one subject who received four doses of morphine 10 mg intravenously at forty-minute intervals. Displacements were calculated assuming parallel slopes. Low doses primarily displaced the curves, whereas larger doses decreased slope as well.

tion is designed to provide a continuous measure of drugs whose effect is primarily a decrease in slope of the CO_2 response curve, for example, the effect of thiopental. Gross, Smith & Smith (15) devised a two-point isohypercapnic technique in which subjects were studied on two separate occasions under

identical circumstances during which $P_{ET}CO_2$ was held constant at 46 mmHg on one occasion and at 58 mmHg on the other. Superimposing the data from these studies provides a continuous two-point curve from which slope can be calculated. The disadvantage of these techniques is their prolonged CO_2 inhalation, which may introduce errors by subject discomfort, apprehension, fatigue, and possibly alteration in CO_2 response by altered buffering capacity.

Response to Hypoxic Stimulation (Hypoxic Response)

Healthy subjects breathe progressively lower oxygen tensions until respiratory stimulation occurs through the carotid body chemoreceptors. The hypoxic stimulus is usually limited to 40 mmHg. To test drug effects on chemoreceptor sensitivity isocapnia must be maintained, because PCO_2 itself alters chemoreceptor sensitivity. CO_2 is therefore added to the inspired gas as ventilation increases, and $P_{ET}CO_2$, $P_{ET}O_2$, and minute volume are measured simultaneously. Steady-state techniques are also used and more rapid rebreathing techniques have been proposed to minimize subject exposure to hypoxia. The curve derived from the plot of $P_{ET}O_2$ and minute ventilation has been described as a hyperbola, although when altered by drugs the curve may be exponential or even flat (Figure 2). Drugs alter the hypoxic response by decreasing the $P_{ET}O_2$ at which respiratory stimulation begins and by decreasing the magnitude of ventilation at all levels of $P_{ET}O_2$. As with CO_2 responses, no single expression incorporates both these changes. Even though gross dose-response relationships have been demonstrated for some anesthetics (Figure 2), the lack of easy quantification inhibits comparisons between drugs and the delineation of dose-response relationships. Further, the position and shape of the curve describing the hypoxic response varies with the level of isocapnia selected, and hypercapnia may increase apparent drug-induced depression of the hypoxic response (16). At the moment, there is no uniformity in methods of measurement of the hypoxic response. Techniques and quantification of these curves as applied to the study of drugs have been treated in greater detail elsewhere (11, 12).

A further confounding aspect of stimulated ventilation curves obtained from drugged subjects is that when sufficiently severe both these stimuli, high PCO_2 and low PO_2, depress the respiratory response through their own actions. In healthy subjects, respiratory depression rather than stimulation probably occurs when PaO_2 is less than 35 mmHg and $PaCO_2$ is greater than 100 mmHg. In drugged subjects, these thresholds may not apply. The slope of the CO_2 response of one subject studied by Johnstone et al (18) was negative when $P_{ET}CO_2$ increased from 70 to 110 mmHg after a large dose of morphine. Kroneberg et al (19) observed hypoxic depression of ventilation at PaO_2 40 mmHg in two healthy subjects who received no drugs.

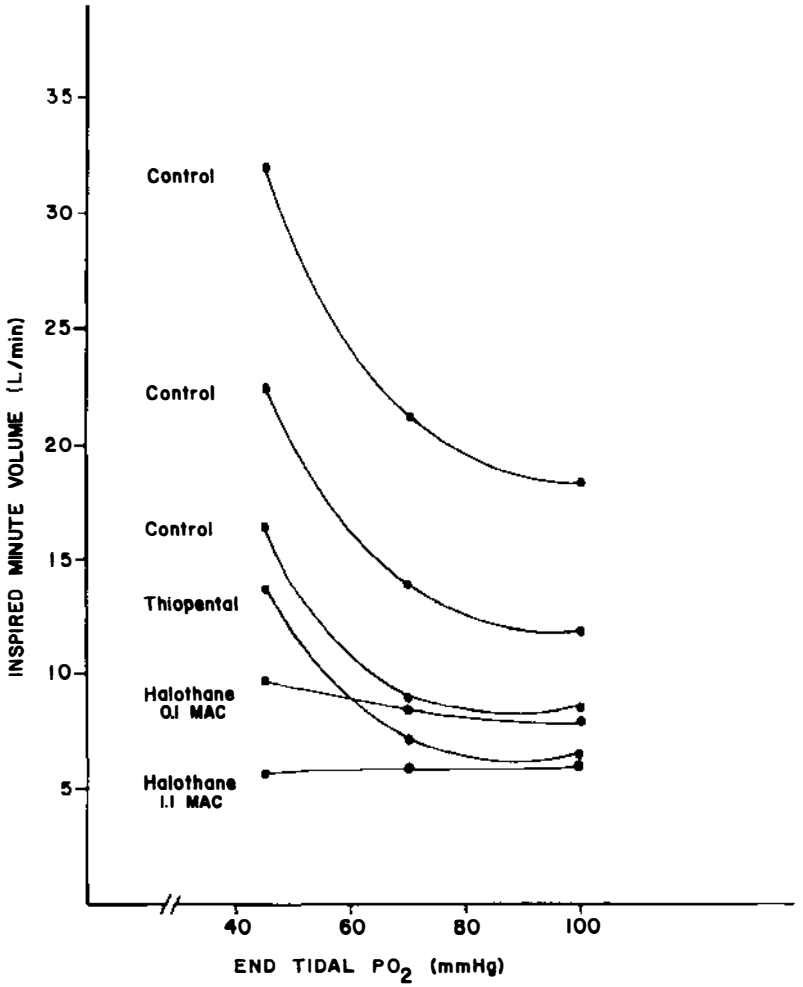

Figure 2 The variety of ventilatory responses to isocapnic hypoxia before and after anesthetics replotted from data of Knill and colleagues (16, 17). The position of control curves is in part related to the level of isocapnia. The topmost curve was the control for the study of thiopental.

SPECIFIC DRUG GROUPS

General Anesthetics

A systematic study of the respiratory and circulatory effects of commonly used inhalation anesthetics was carried out by E. I. Eger II and his colleagues over a period of a decade.

CO_2 RESPONSE Eger and colleagues employed healthy subjects on whom no operation was performed and obtained quantitative comparisons between drugs

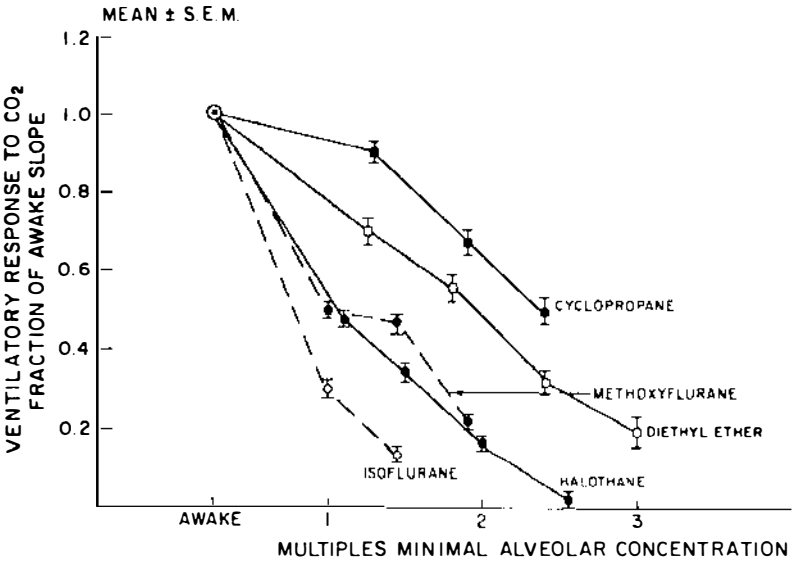

Figure 3 The relationship between doses of various inhaled anesthetic agents and the percent of depression of the slope of the CO_2 response (20, 21). Dose is expressed in multiples of MAC (see text). [Reproduced from (5) with permission.]

and dose-response relationships for each drug. Most of their data were summarized in one publication (20), and subsequently data on isoflurane were added (21). These are summarized in Figures 3 and 4. Dose was expressed as multiples of MAC, the minimal alveolar (end-tidal) concentration of inhaled anesthetic at steady state that prevented movement in response to a surgical skin incision in 50% of patients. The MAC value for each anesthetic had been determined previously in patients undergoing operations. The dose scale is presented linearly and represents multiples of the MAC dose. In equipotent anesthetic doses, isoflurane is the most potent respiratory depressant. Except for diethylether, the increase in $PaCO_2$ during anesthesia with spontaneous ventilation correlated well with depression of the slope of the CO_2 response. The ability of subjects to maintain normocapnia while spontaneously breathing diethylether up to 3 MAC suggests that stimulation of peripheral chemoreceptors or mechanical receptors in the lung or airway, or of those responsive to the irritant properties of diethylether, increases respiratory center input while sensitivity of the center progressively decreases.

HYPOXIC RESPONSE Recently, the remarkable sensitivity of the chemoreceptor mechanism to depression by inhalation anesthetics was demonstrated by Knill and his colleagues. Their results, together with those of Yacoub et al (22), are summarized in Table 1. Depression of chemoreceptor sensitivity

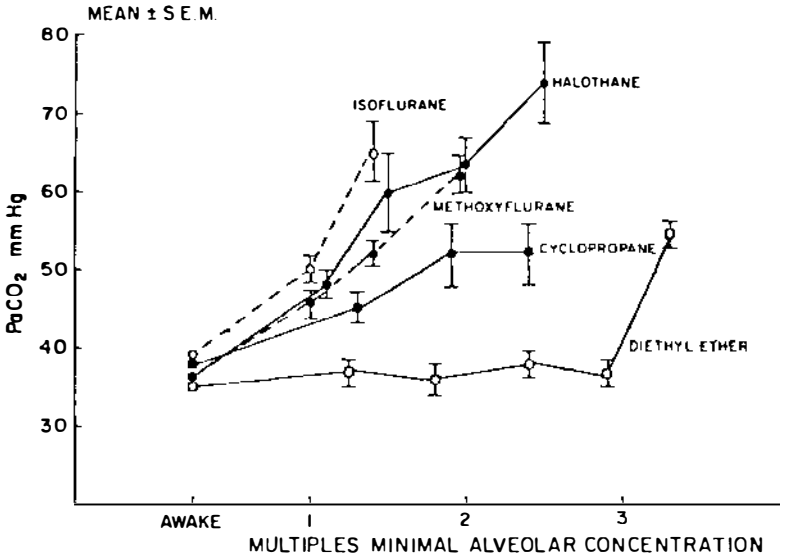

Figure 4 The relationship between doses of various inhaled anesthetic agents and $PaCO_2$ during spontaneous respiration (20, 21). Note the lack of dose-effect relationship for diethylether. [Reproduced from (5) with permission.]

was almost identical for the three fluorinated hydrocarbons. The site of depression was confirmed by measuring the marked reduction by these anesthetics in the ventilatory response to a small intravenous dose of doxapram, known to stimulate the chemoreceptor mechanism primarily (16, 24). During these studies, responsiveness to the CO_2 stimulus in terms of depression of slope of the CO_2 response was also measured. CO_2 response did not decrease at doses that depressed the hypoxic response (0.1 MAC) and was still present, although decreased, at doses that abolished the hypoxic response (1.1 MAC). An overview of the effect of fluorinated hydrocarbons on respiration is summarized in Figure 5.

INTRAVENOUS ANESTHETICS Measurement of respiratory effects of intravenous anesthetics has been difficult because of the absence of a steady state owing to rapid drug redistribution. Knill et al (17) studied thiopental given by infusion at rates that maintained either clinical sedation (drowsy, conscious) or anesthesia (loss of eyelid reflex). Sedative doses of thiopental did not alter the CO_2 response or the hypoxic response. However, anesthetic doses depressed both responses, as well as the response to doxapram, to approximately the same degree. The nonspecific depression of responses by thiopental contrasts with the selective chemoreceptor depression by inhaled anesthetics, indicating quantitatively different actions on the components of ventilatory control.

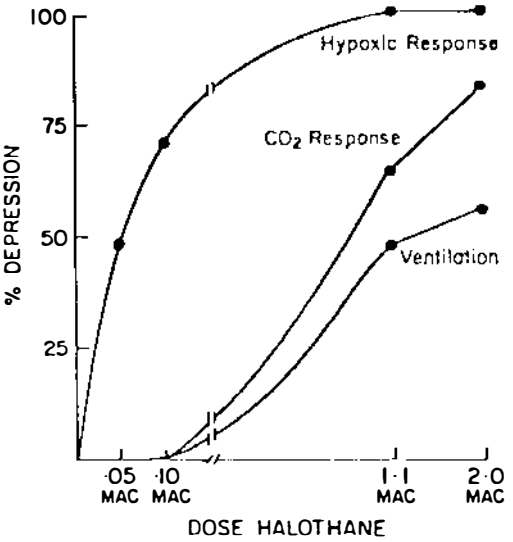

Figure 5 Dose-related effects of halothane on the hypoxic response, the CO_2 response, and on spontaneous ventilation. The lower doses (0.05–0.1 MAC) do not produce unconsciousness, whereas the two higher doses produce general anesthesia. The extreme sensitivity of the hypoxic response to halothane is demonstrated. [Reproduced from (23) with permission.]

Attempts to find alternatives to thiopental as an intravenous induction agent for general anesthesia led to a trial of diazepam and more recently to a trial of a water-soluble benzodiazepine, midazolam, for this purpose. Early studies of changes in resting ventilation or arterial blood gases by diazepam given by mouth or intramuscularly were equivocal on respiratory depressant activity.

Table 1 Effect of anesthetics on ventilatory response to hypoxia

Drug	Dose	Response	Reference
Nitrous oxide	30–50%	Depressed	22
Halothane	0.05 MAC[a]	Depressed	23
	0.1 MAC	Depressed	16, 23
	1.1 MAC	Abolished	16
	2.0 MAC	Abolished	16
Enflurane	0.1 MAC	Depressed	24
	1.1 MAC	Abolished	24
Isoflurane	0.1 MAC	Depressed	25
	1.1 MAC	Abolished	25
Thiopental	Sedation	None	17
	Anesthesia	Depressed	17

[a] Minimal alveolar concentration (see text for definition).

When given intravenously, however, in doses of 0.1–0.4 mg/kg, diazepam showed a consistent decrease of about 50% in the slope of the CO_2 response, with peak effect approximately 30 minutes after administration (15, 26, 27). Forster et al (27) compared diazepam 0.3 mg/kg with midazolam 0.15 mg/kg, both given intravenously, and found that they depressed the CO_2 response equally. Gross et al (28), using the dual isohypercapnic technique, compared midazolam 0.2 mg/kg with thiopental 3.5 mg/kg given intravenously to healthy subjects and to patients with chronic obstructive pulmonary disease. Both drugs significantly depressed the slope of the CO_2 response. Depression was greater after midazolam than after thiopental, and both drugs produced greater depression in patients with obstructive pulmonary disease. Curiously, Power et al (29) were unable to find any significant alteration in the CO_2 response after administering midazolam 0.075 mg/kg or diazepam 0.15 mg/kg intravenously.

Jordan et al (26) claim to have shortened the respiratory depression of diazepam 0.2 mg/kg by giving naloxone 15 mg 60 minutes and again 95 minutes after diazepam compared to similarly administered placebo. Forster et al (30) observed no antagonism when naloxone 1 mg was given five minutes after midazolam in doses up to 0.2 mg/kg intravenously. Clearly, diazepam receptors are different from naloxone receptors.

Narcotic Analgesics

Borison (4) in his review tabulated the available references to drug effects on respiration in man by specific drug, identifying those that studied the CO_2 response and those that studied components of resting ventilation. His table provides a convenient reference source for narcotic analgesics as well as for antagonists. Tilidine can now be added to that list (31).

CO_2 RESPONSE Most investigations on CO_2 response have been generated by a search for potent analgesics with a lesser side action liability than morphine. The pattern was an initial determination of analgesic potency, usually in postoperative pain, followed by measurement of the respiratory depressant capacity of equianalgesic doses in terms of displacement of the CO_2 response. In contrast to the primary effects of anesthetics and drugs producing sleep on the slope of the CO_2 response, narcotic analgesics primarily displaced response to the right, with statistically insignificant changes in slope. With almost boring consistency, drugs of this type produce equivalent respiratory depression when given in equianalgesic doses (Table 2). Drugs of this type have been identified as μ agonists in opiate receptor terminology.

HYPOXIC RESPONSE Surprisingly, of the narcotic analgesic compounds only morphine and meperidine have been studied for their effect on the hypoxic response. Weil et al (32) described depression of this response one hour after

Table 2 Doses of clinically used potent analgesics that produce equal analgesia and respiratory depression in man by the intramuscular route

Analgesic	Dosage
Morphine	10 mg
Meperidine	75 mg
Methadone	10 mg
Anileridine	30 mg
Oxymorphone	1 mg
Levorphanol	2.5 mg
Alphaprodine	30 mg
Hydromorphone	1.2 mg
Oxycodone	14 mg
Dihydrocodeine	60 mg
Heroin	5 mg
Fentanyl	0.15 mg
Codeine	~ 120 mg

administering morphine 7.5 mg subcutaneously. The degree of depression was similar to that shown for thiopental in Figure 2. Kryger et al (33) demonstrated a depressed hypoxic response two hours after meperidine 1.2 mg/kg was given by mouth. Like thiopental and unlike the inhalation anesthetics, the magnitude of depression of the hypoxic response and the CO_2 response was approximately equal.

ORAL ADMINISTRATION The paucity of studies of the respiratory effects of analgesics given by mouth is surprising in view of the abundant studies of analgesic potency by this route. Only Bellville and his associates have pursued this question with any consistency. In a nicely designed study, they determined that the respiratory effect of codeine 100 mg was equal to that of morphine 10 mg when both were given intramuscularly (34). They then determined that oral codeine was 0.72 as potent as intramuscular codeine in terms of respiratory depression. By extrapolation, they estimated codeine 140 mg orally to be the respiratory depressant equivalent of morphine 10 mg intramuscularly. From their companion study on the respiratory effects of oral dextropropoxyphene and codeine, they estimated by extrapolation that 420 mg of dextropropoxyphene would be required by mouth to depress respiration as much as morphine 10 mg intramuscularly (35). Meperidine 1.2 mg/kg by mouth depressed the CO_2 response as well as the hypoxic response (33).

AS AN ANESTHETIC SUPPLEMENT During the past fifteen years, narcotic analgesics have been increasingly used as supplements during general anesthe-

sia, usually with nitrous oxide. For forty years, meperidine was the traditional drug for this purpose, usually given in 100 to 200 mg doses. Recently, morphine in doses up to 2 mg/kg and fentanyl up to 100 μg/kg have been used to supplement general anesthesia. At times even higher doses, with oxygen alone and with a neuromuscular blocking drug, have been administered as general anesthesia for cardiac operations. The attraction of these techniques, which incorporate very large narcotic doses, is their relative freedom from hemodynamic effects compared to halogenated hydrocarbons. Their drawback is their failure to block the hemodynamic responses to surgical stimulation and, when adequate hypnotic drugs have not been added, the potential of an aware but immobilized patient during operations. Current preference is for fentanyl because of its high milligram potency, rapid onset of action, and short duration. When given as small single doses intravenously to healthy subjects, fentanyl (1.4 μg/kg given over 2.5 minutes) depressed the CO_2 response for a shorter period than alphaprodine or meperidine (14). Time to peak effect, however, was the same for all three drugs, about eight minutes. With a much larger dose of fentanyl (6.4 μg/kg given over 90 seconds) peak respiratory depression in terms of $P_{ET}CO_2$ during spontaneous respiration developed in less than five minutes and returned to control over the next four hours (36). The rate of decrease in $P_{ET}CO_2$ correlated well with the rapid rate of decline in plasma fentanyl levels. Within sixty minutes 98.6% of the fentanyl dose was eliminated from the plasma and terminal half-life was 3.6 hours (37). Recovery from fentanyl-induced respiratory depression occurs primarily by redistribution rather than by drug elimination. As expected with these pharmacokinetic characteristics, the larger the initial dose the more rapid the onset of respiratory depression and the greater its persistence.

Stoeckel et al (38) administered 0.5 mg (approximately 8 ug/kg) to seven healthy subjects, three of whom became apneic for 2–7 minutes. Their CO_2 response did not return to control within the six hours of study. While noting that respiratory depression correlated with plasma fentanyl levels, they found secondary increases in plasma fentanyl 45–90 minutes after intravenous injection. In two subjects, the increase was sufficient to induce a recurrence of severe respiratory depression. This suggested an entero-systemic recirculation of fentanyl as a possible mechanism, since the researchers observed gastric secretion of fentanyl for thirty minutes after the initial dose (39). Adams & Pybus (40) observed severe postoperative respiratory depression in three of their patients after apparent recovery from a general anesthetic that included modest doses of fentanyl. The time course of depression in their patients does not fit the entero-systemic recirculation mechanism described for healthy subjects. The more likely cause of recurrent respiratory depression was the same as that described by Becker et al (41) and inappropriately labeled biphasic respiratory depression. Becker et al (41) noted that patients who received

fentanyl during operations and apparently recovered CO_2 responsiveness afterward suffered recurrent depression of the CO_2 response when left unstimulated in the postoperative period. Surgical stimulation, pain, noise, movement, and wakefulness are well-known antagonists of the decreased CO_2 responsiveness induced by narcotic analgesics.

Even more prolonged respiratory depression after fentanyl was measured in anesthetized patients in whom pharmacokinetics may have been disturbed by alterations in hepatic blood flow, body temperature, concomitant drugs and prolonged hypocarbia (42). Clearly, fentanyl in doses used for anesthetic supplementation is not short acting and a search is underway among its analogues (alfentanil, sufentanil, lofentanil) for equally potent compounds with a better pharmacokinetic profile (43).

Narcotic Antagonists

CO_2 RESPONSE

With the discovery of the analgesic activity of nalorphine, the search for an improved analgesic extended to the narcotic antagonists, now known as κ agonists in opiate receptor terminology. As with narcotic analgesics, analgesic activity is quantitatively linked to respiratory depressant activity in an almost obligatory relationship (Table 3). References to early data on respiratory depression by narcotic antagonists are summarized in (4). There are no studies of effects of narcotic antagonists on the hypoxic response.

A possible exception to this seemingly obligatory relation is meptazinol, a narcotic antagonist with minimal respiratory effects in doses that produce analgesia equivalent to morphine and pentazocine in man. Receptor binding studies reviewed by Snyder (48) suggest meptazinol may be a specific agonist at the μ_1 receptor implicated in analgesia but not in respiratory depression. That meptazinol is without respiratory depressant activity is not particularly clear from the studies summarized by Jones (49). In a crossover study of healthy subjects, morphine, pentazocine, and diazepam decreased the slope of the CO_2 response, whereas meptazinol and placebo did not. However, meptazinol, like morphine and pentazocine, increased $P_{ET}CO_2$ during breathing at rest and

Table 3 Doses of narcotic antagonist analgesics that produce equal analgesia and respiratory depression in man

Analgesic	Dosage	Reference
Nalorphine	10 mg	
Pentazocine	30–40 mg	
Nalbuphine	10 mg	44
Butorphanol	2 mg	45
Buprenorphine	0.4 mg	46
Dezocine	10 mg	47

breathing against an inspiratory load, whereas diazepam and placebo did not increase $P_{ET}CO_2$.

CEILING EFFECT FOR RESPIRATORY DEPRESSION One difference between narcotic analgesic and antagonist effects on respiration became apparent when the dose-response relationships for nalorphine was explored (50). Displacement of the CO_2 response by nalorphine was dose related until cumulative intravenous increments reached 30 mg/70 kg, after which no further displacement occurred despite doubling the dose. This ceiling effect for respiratory depression has now been demonstrated for two other narcotic antagonist analgesics (47) (Figure 6).

Whether this ceiling effect is characteristic of all narcotic antagonist analgesics is not yet clear, since data are not available at the higher doses necessary to establish a ceiling. Available data on pentazocine and butorphanol suggest that the slope of the dose-effect curve for respiratory depression is less than that for morphine, but no ceiling has been achieved. Sufficient data on buprenorphine are not available. The respiratory-depressant data on meptazinol cited earlier could be interpreted as typical of narcotic antagonist analgesics, but with a ceiling so low as to be undetected by changes in the slope of the CO_2 response in distinction to changes in displacement.

An interesting analogy to this ceiling effect for respiratory depression by narcotic-antagonist analgesics is the ceiling effect for analgesia demonstrated in animals in terms of their anesthesia-sparing effects. The end tidal concentration of inhalation anesthetic agents necessary to maintain a fixed depth of general anesthesia is reduced by both narcotics and narcotic antagonists. When the degree of reduction in end tidal anesthetic concentration is measured during cumulative increments of intravenous narcotic (morphine or fentanyl), anesthetic concentrations can be reduced by a maximum of 65% (ceiling effect). By contrast, in this model the ceiling effect of butorphanol, nalbuphine, and pentazocine showed only a 10–20% reduction (51, 52).

ANTAGONISM OF NARCOTIC AND NARCOTIC ANTAGONIST–INDUCED RESPIRATORY DEPRESSION Naloxone, nalorphine, and levallorphan are as effective in antagonizing the respiratory depressant effects of nalbuphine as of morphine (44). Initial peak antagonism by naloxone is more complete than by the other two antagonists and occurs within fifteen minutes. At times respiration transiently exceeds normal control respiration (overshoot). After peak antagonism by naloxone, respiratory depression returns over thirty minutes to a level below peak depression, and residual depression wanes over the next two to three hours. This pattern is in accord with the rapid redistribution of naloxone. Although the general pattern of antagonism is the same, peak antagonism is less intense after the administration of levallorphan or nalor-

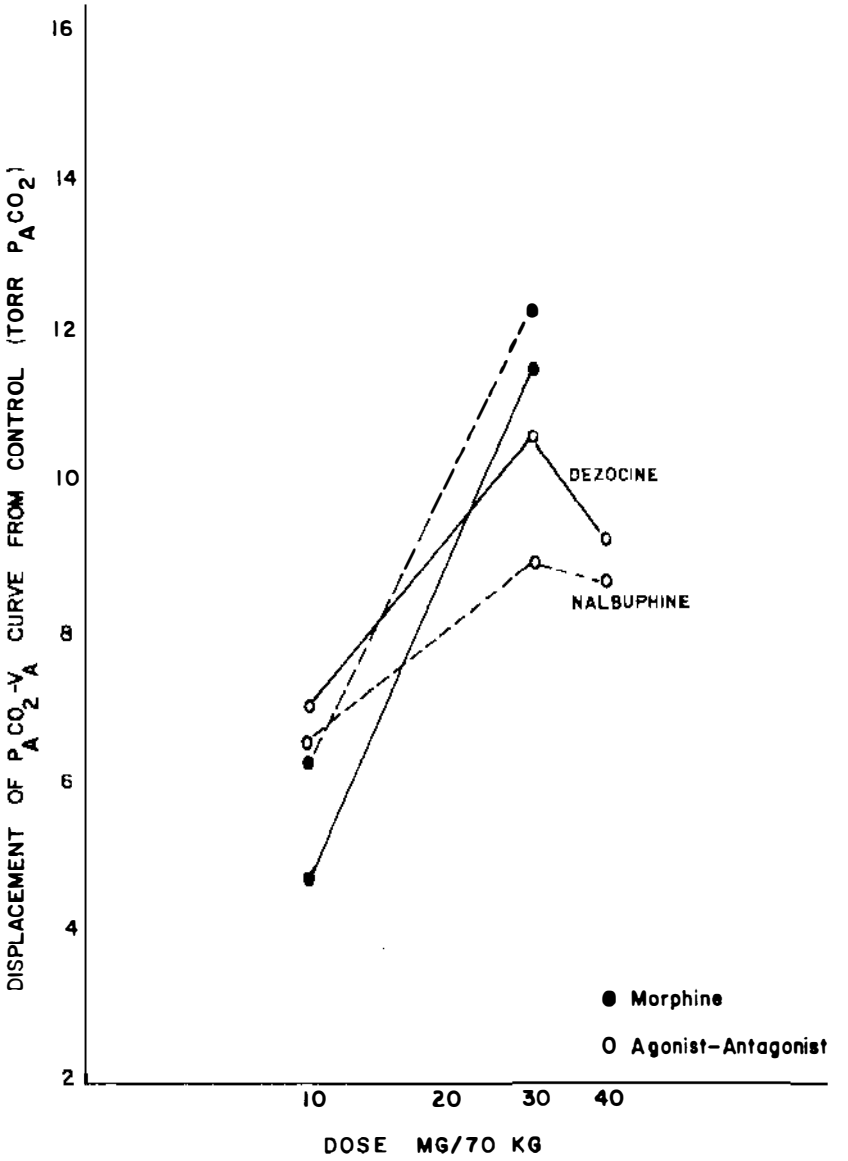

Figure 6 Dose-effect curves for respiratory depression by cumulative doses of morphine, dezocine, and nalbuphine. All three drugs produce equal analgesia in man at 10 mg/70 kg. The ceiling effect for respiratory depression by dezocine and nalbuphine and the lesser slope of their dose-response curves contrast with the morphine curves. Two separate groups of subjects were studied and are identified by solid and dashed lines. [Reproduced from (47) with permission.]

phine, both of which have intrinsic respiratory-depressant activity in contrast to naloxone. The usual explanation for this phenomenon is that the antagonist with its greater affinity substitutes its own agonist-respiratory effect for the drug displaced at the receptor in accord with competitive dualism theory. This interpretation is supported by studies of the interactions on respiration in man between morphine and nalorphine (53), meperidine and levallorphan (54), and oxymorphone and naloxone (55). The lack of agonist activity of naloxone and the intense respiratory and circulatory stimulation that follows its administration has led to serious complications when it is given after anesthesia supplemented by large doses of narcotics. These included hypertension, dysrhythmias, ruptured cerebral aneurysm, and especially pulmonary edema, both in patients with heart disease and in healthy young adults (56). Sudden death under these circumstances has also been reported (57). With the increasing use of narcotic supplementation of general anesthesia, there is sentiment for antagonizing-respiratory depression after operations with antagonists that possess analgesic and respiratory depressant agonist actions, such as nalbuphine or buprenorphine. The latter drug is poorly antagonized by naloxone, however (46).

Hypnotics and Tranquillizers

A major concern in introducing hypnotics and tranquillizers into clinical use is their potential toxicity in attempted suicide. Despite this, the respiratory effects of these compounds, particularly in the higher than therapeutic dose range, are rarely explored. Most relevant studies are limited to therapeutic doses or effects when the classes are combined with narcotics, with little concern for equieffective dose or dose-response relationships. Available data as they apply to a variety of doses unrelated to therapeutic equivalence can be summarized briefly.

HYPNOTICS The respiratory effects of barbiturate hypnotics are similar to the effects of intravenous thiopental cited earlier. In sedative doses, thiopental produced no measurable effect on respiration; in anesthetic doses, both the CO_2 response and the hypoxic response were depressed equally. Pentobarbital 150 mg (58) but not secobarbital 100 mg (59), both given intramuscularly, modestly depressed the CO_2 response of healthy subjects. Cyclobarbital in doses of 200–600 mg by mouth did not depress the CO_2 response but slightly depressed the hypoxic response at the highest dose (60). Pentobarbital 2 mg/kg intramuscularly depressed the response to hypoxia in five of ten subjects and had no effect in the other five (61). Triclofos 1–3 gm and ethchlorvynol 500 mg by mouth had no respiratory effects (60), but chloralhydrate 20 mg/kg by mouth increased resting $PaCO_2$ of nonasthmatic patients 5 mmHg and 10 mmHg in asthmatic patients (62).

BENZODIAZEPINES As described above, diazepam 0.1–0.4 mg/kg intravenously consistently depressed CO_2 response. Diazepam 7.5 and 15 mg intramuscularly displaced the CO_2 response curve almost as much as pentazocine 30 mg (63). Benzodiazepines that failed to affect the CO_2 response include: chlordiazepoxide 1 mg/kg intramuscularly (64), lorazepam 4 mg intramuscularly (58), lorazepam 3.5 mg intravenously (65), triazolam 0.5 mg orally (66). Temazepam 40 mg orally depressed the CO_2 response (67). Flurazepam 15 mg but not nitrazepam 5 mg, both given orally, decreased the CO_2 response of healthy subjects and patients with bronchitis (68). However, nitrazepam 10 mg by mouth given nightly for five days increased resting $PaCO_2$ and depressed the CO_2 response of patients with chronic bronchitis (69). The seeming lack of respiratory depressant activity of many benzodiazepines may be dose related, and depression may become more apparent only in patients with impaired ventilation or in overdosage.

NARCOTIC TRANQUILLIZER MIXTURES Mixtures of phenothiazines and narcotics were first explored in the hope that analgesia would be potentiated by relief from anxiety and that respiratory depression would be lessened by a decrease in narcotic dose. Despite the common clinical use of these combinations, no enhanced analgesia with lesser respiratory depression was ever demonstrated. The addition of a phenothiazine prolongs and to a small degree increases the respiratory depression of the narcotic component, with a large increase in associated sedation by additive effects. This general result followed when meperidine was combined with chlorpromazine (70), promethazine (71), or propriomazine (72) and when prochloroperazine was added to morphine (73). Phenothiazines given alone may slightly depress the CO_2 response (70, 72), but this has usually been difficult to document because of the restlessness they induce in healthy subjects when given as the sole drug (71, 73). When benzodiazepines were combined with meperidine, neither chlordiazepoxide 1 mg/kg (64) nor lorazepam 0.05 mg/kg intravenously (65) added to the meperidine depression of the CO_2 response.

Fentanyl was introduced clinically in combination with droperidol as Innovar® for use as an anesthetic supplement and for preanesthetic medication. Droperidol, a butyrophenone, was intended to add sedation, a reduction in responsiveness to environmental stimuli, and an antiemetic activity to the narcotic effects of fentanyl. Droperidol did not increase the depression of the CO_2 response by fentanyl (74). Interest in the respiratory effects of droperidol has been renewed recently as a result of the observation that dopamine by infusion slightly increased resting $PaCO_2$ but markedly decreased the hypoxic response in normal man without an effect on the CO_2 response (75). Assuming that dopamine is an inhibitory neurotransmitter at the carotid body, further studies showed complete block of this response to dopamine by haloperidol

(76) and droperidol (77), both dopamine antagonists. Droperidol increased the normal response to hypoxia (77) but did not alter the response to CO_2 (78).

Other Related Drugs

Hydroxyzine, a minor tranquillizer and antiemetic used primarily for relief of anxiety and sedation, is unique in possessing analgesic activity in the range of morphine combined with modest respiratory depressant activity. The depression of the CO_2 response by hydroxyzine is additive to that of pentazocine (79) and is not antagonized by naloxone (80).

Δ-9-tetrahydrocannabinol when smoked (81), taken orally (81), or given intravenously (82) in doses that produced marked psychological impairment depressed the CO_2 response only slightly. In these same subjects, 180 ml alcohol or 150 mg pentobarbital by mouth did not affect the CO_2 response (81). When given intravenously with pentobarbital 100 mg/70 kg, tetrahydrocannabinol produced no respiratory depression (83). When it was given with oxymorphone 1 mg/70 kg, the effect on the CO_2 response was additive.

Well-designed studies have shown that a bolus of lidocaine 100 mg administered intravenously depressed the CO_2 response for two minutes after administration (84) and cimetidine 600 mg orally intensified and prolonged the depression of CO_2 response by morphine 10 mg intramuscularly (85).

OTHER CONSIDERATIONS

Drug Effects in Patients with Pulmonary Disease

Despite the special relevance of administering respiratory depressants to patients in whom a small drug effect may have a profound clinical effect, relatively few studies have been carried out in this population. One reason is that methods useful in healthy subjects do not apply to patients with severe airway disease, e.g. chronic obstructive pulmonary disease or asthma, because mechanical limitations prevent adequate responses to CO_2 or hypoxic stimulus. For example, Gold et al (86) attempted to measure the effects of pentobarbital 100 mg orally in nine bronchitic patients. The mean slope of their predrug CO_2 response curve was only 15% of the slope of a group of normal subjects tested by the same method. Although the slope was not altered by pentobarbital, the hypnotic effect of pentobarbital was so great in these patients that two of five who fell asleep developed respiratory failure. Forrest & Bellville (87) were the first to describe the potentiation by sleep of morphine effects on the CO_2 response. Sleep not only increased displacement but markedly reduced slope, suggesting a mechanism for the respiratory failure observed.

Methods to measure respiratory center output in response to a CO_2 stimulus have been devised for patients unable to generate the ventilation response because of disease. These methods measure the negative pressure generated at

the beginning of inspiration, when the airway is transiently occluded, usually for 100 msec. The measurement is referred to as mouth occlusion pressure ($P_{0.1}$). In healthy subjects, occlusion of this duration is insufficient to interfere with the ventilatory response to CO_2, is independent of pulmonary mechanics, and is linearly related to $P_{ET}CO_2$ in the same manner as is the ventilatory response. In healthy subjects, drugs that depress the slope of the CO_2 response depress the slope of the mouth occlusion pressure response to the same degree (26, 27). In the only study in which this method was applied to the study of drugs in patients with pulmonary disease, diazepam 20 mg per day for two days depressed the $P_{0.1}$ response, whereas prazepam at the same dose did not alter the response (88).

A second approach to the estimation of drug effects in patients with lung disease is to simulate airway disease in healthy subjects by adding some resistance to inspiration while stimulating respiration by CO_2 or hypoxia. The effect of the load is to prolong inspiration while maintaining normal minute volume and frequency of respiration. Response to the load can be measured in terms of gas exchange volumes, blood gases, or mechanical properties of the chest. Since consciousness is an important aspect of maintaining ventilation during inspiratory loading, drugs that alter consciousness markedly effect this response independent of a respiratory control center effect. The suitability of this model for predicting drug effects in patients with lung disease is not yet clear. Jordan (11) has reviewed these methods as they apply to study of drugs in greater detail.

New Approaches to Pain Therapy and Respiratory Depression

Stimulated by new knowledge of opioid peptides occuring normally in the central nervous system, small milligram doses of narcotic analgesics were introduced intrathecally or epidurally in man and found to produce analgesia lasting as long as twenty-four hours. Enthusiasm for the potential of this technique in pain control has led to numerous publications, which have been recently summarized and well reviewed by Martin et al (89). Although morphine has been used most commonly, meperidine, methadone, hydromorphone, heroin, and fentanyl are also effective analgesics by this route. One of the major adverse reactions is the recurrence or delayed onset of severe respiratory depression, which appears 8–10 hours after administration. It is now clear from pharmacokinetic studies that drug absorption from the epidural or intrathecal spaces is approximately comparable to absorption from intramuscular administration. Onset of early respiratory depression relates primarily to the lipophilic characteristics of the drug, and duration approximates that expected from intramuscular administration. The delayed respiratory depression is unrelated to plasma levels, however, and is therefore attributed to the rostral spread of the drug within the subarachnoid space, reaching sensitive structures in the fourth ventricle. Kafer et al (90) nicely demonstrated distinct

early and delayed respiratory depression two hours and eight hours after morphine 0.1 mg/kg was administered epidurally. Probably both mechanisms act in continuous fashion in most patients, since continuously depressed ventilation persisting for 17–22 hours without early and late peaks has been demonstrated after 10 mg of epidural morphine (91, 92). The tendency toward rostral spread may be less with more lipophilic drugs (93). Among the narcotic antagonists, only pentazocine has been administered in this manner; it produced effective prolonged analgesia by the epidural route (94).

Other new approaches to the control of pain include continuous infusion and the patient-controlled techniques of intravenous administration of potent analgesics. Both techniques require reasonable knowledge of the pharmacokinetics of the compounds administered. To increase the safety of these techniques, investigators have attempted to define blood levels that produce analgesia and those related to important respiratory depression (42, 95). Not surprisingly, a wide range of blood values have been associated with similar degrees of respiratory depression, even though blood level and magnitude of respiratory depression roughly correlate. Considering the potentially large alterations in the pharmacokinetics of patients with disease and surgical operation, the large variation in pain experienced by patients, and the large variation in individual sensitivity to the respiratory and analgesic effects of potent analgesics, probably no more than rough correlations can be expected between blood levels, analgesia, and respiratory depression.

Respiratory Stimulants

Doxapram remains the only respiratory stimulant available for this specific indication in patients with respiratory depression or failure. Although doxapram has been assumed to act entirely by increasing sensitivity of the peripheral chemoreceptors, Calverley et al (96) recently demonstrated a marked increase in slope of the CO_2 response in healthy subjects as well as an increase in the hypoxic response, suggesting a central action as well for doxapram. The ability of doxapram to antagonize morphine-induced respiratory depression has not been determined. Other compounds, however, presumably acting by control center stimulation, have partially antagonized the CO_2 response depressed by morphine. These include methylphenidate (97), caffeine (98), benzquinamide (73), and dextroamphetamine (99). Both physostigmine (100) and aminophylline (101) have partially antagonized respiratory effects by mechanisms that are not clear.

SUMMARY

This review has consisted largely of studies of drug effects in healthy subjects undertaken quite properly to explore unknown actions of a variety of com-

pounds administered by different routes. Limitations have been noted throughout, including the lack of standardization of methods and of treating data, a failure to explore effects other than the CO_2 response, and especially a failure to explore dose-response relationships. There is, however, a more serious criticism: the lack of studies of these same compounds in patients with disease for whom their use was intended. Such studies may require other methods, some of which have been suggested by Jordan (11). Extrapolation of data from healthy subjects to patients with disease may be difficult, but such data indicate what to look for. Considering the diversity of disease factors potentially affecting respiration, the interaction of drugs and disease other than pulmonary disease is a fruitful area for exploration. Responses to CO_2 and/or hypoxia are altered in congenital heart disease and in carotid artery occlusive disease, by progesterone during pregnancy, by acid-base disorders caused by or secondary to chronic diuretic therapy or chronic aspirin ingestion, in semistarvation, and by level of protein intake. Drug actions on respiration in disease states are almost unexplored.

Literature Cited

1. Lambertsen, C. J. 1966. Drugs and respiration. *Ann. Rev. Pharmacol.* 6:327–78
2. Brown, E. B. Jr. 1971. Drugs and respiratory control. *Ann. Rev. Pharmacol.* 11:271–84
3. Borison, H. L. 1977. Central nervous respiratory depressants—Control systems approach to respiratory depression. *Gen. Syst. Pharmacol.: Pharmacol. Ther. Part B* 3(2):211–26
4. Borison, H. L. 1977. Central nervous respiratory depressants—Narcotic analgesics. See Ref. 3, pp. 227–37
5. Kafer, E. R., Marsh, H. M. 1977. The effect of anesthetic drugs and disease on the chemical regulation of ventilation. In *Anesthesia and Respiratory Function. International Anesthesiology Clinics,* ed. E. R. Kafer, 15:1–38. Boston: Little, Brown
6. Schlitt, S. C., Schroeter, L. M., Wilson, J. E., Olsen, G. D. 1978. Methadone-induced respiratory depression in the dog: Comparison of steady-state and rebreathing techniques and correlation with serum drug concentration. *J. Pharmacol. Exp. Ther.* 207:109–22
7. Bellville, J. W., Seed, J. C. 1960. Effect of drugs on the respiratory response to carbon dioxide. *Anesthesiology* 21:727–41
8. Keats, A. S. 1966. Evaluation of respiratory depressant capacity. In *International Encyclopedia of Pharmacology and Therapeutics,* ed. L. Lasagna, 1:133–54. New York: Pergamon
9. Jennett, S. 1968. Assessment of respiratory effects of analgesic drugs. *Br. J. Anaesth.* 40:746–56
10. Smith, T. C. 1971. Pharmacology of respiratory depression. In *Pharmacologic Topics in Anesthesiology. International Anesthesiology Clinics,* ed. R. A. Miller, 9:125–43. Boston: Little, Brown
11. Jordan, C. 1982. Assessment of the effects of drugs on respiration. *Br. J. Anaesth.* 54:763–82
12. Saunders, K. B. 1980. Methods in the assessment of the control of breathing. *Br. J. Clin. Pharmacol.* 9:3–9
13. Lambertsen, C. J., Wendel, H. 1960. An alveolar pCO_2 control system: Its use to magnify respiratory depression by meperidine. *J. Appl. Physiol.* 15:43–48
14. Kaufman, R. D., Aqleh, K. A., Bellville, J. W. 1979. Relative potencies and durations of action with respect to respiratory depression of intravenous meperidine, fentanyl and alphaprodine in man. *J. Pharmacol. Exp. Ther.* 208:73–79
15. Gross, J. B., Smith, L., Smith, T. C. 1982. Time course of ventilatory response to carbon dioxide after intravenous diazepam. *Anesthesiology* 57:18–21
16. Knill, R. L., Gelb, A. W. 1978. Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anes-

thesia in man. *Anesthesiology* 49:244–51
17. Knill, R. L., Bright, S., Manninen, P. 1978. Hypoxic ventilatory responses during thiopentone sedation and anesthesia in man. *Can. Anaesth. Soc. J.* 25:366–72
18. Johnstone, R. E., Jobes, D. R., Kennell, E. M., Behar, M. G., Smith, T. C. 1974. Reversal of morphine anesthesia with naloxone. *Anesthesiology* 41:361–67
19. Kronenberg, R., Hamilton, F. N., Gabel, R., Hickey, R., Read, D. J. C., Severinghaus, J. 1972. Comparison of three methods for quantitating respiratory response to hypoxia in man. *Respir. Physiol.* 16:109–25
20. Larson, C. P., Eger, E. I. II, Muallem, M., Buechel, D. R., Munson, E. S., Eisele, J. H. 1969. The effects of diethylether and methoxyflurane on ventilation: A comparative study in man. *Anesthesiology* 30:174–84
21. Fourcade, H. E., Stevens, W. C., Larson, C. P., Cromwell, T. H., Bahlman, S. H., et al. 1971. The ventilatory effects of forane, a new inhaled anesthetic. *Anesthesiology* 25:26–31
22. Yacoub, O., Doell, D., Kryger, M. H., Anthonisen, N. R. 1976. Depression of hypoxic ventilatory response by nitrous oxide. *Anesthesiology* 45:385–89
23. Gelb, A. W., Knill, R. L. 1978. Subanesthetic halothane: Its effect on regulation of ventilation and relevance to the recovery room. *Can. Anaesth. Soc. J.* 25:488–94
24. Knill, R. L., Manninen, P., Clement, J. L. 1979. Ventilation and chemoreflexes during enflurane sedation and anesthesia in man. *Can. Anaesth. Soc. J.* 26:353–60
25. Knill, R. L., Kieraszewicz, H. T., Dodgson, B. G., Clement, J. L. 1983. Chemical regulation of ventilation during isoflurane sedation and anesthesia in humans. *Can. Anaesth. Soc. J.* 30:607–14
26. Jordan, C., Lehane, J. R., Jones, J. C. 1980. Respiratory depression following diazepam: Reversal with high dose naloxone. *Anesthesiology* 53:293–98
27. Forster, A., Gardaz, J., Suter, P. M., Gemperle, M. 1980. Respiratory depression by midazolam and diazepam. *Anesthesiology* 53:494–97
28. Gross, J. B., Zebrowski, M. E., Caral, W. D., Gardner, S., Smith, T. C. 1983. Time course of ventilatory depression after thiopental and midazolam in normal subjects and in patients with chronic obstructive pulmonary disease. *Anesthesiology* 58:540–44
29. Power, S. J., Morgan, M., Chakrabarti, M. K. 1983. Carbon dioxide response curves following midazolam and diazepam. *Br. J. Anaesth.* 55:837–41
30. Forster, A., Morel, D., Bachmann, M., Gemperle, M. 1983. Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone-A double blind randomized study. *Anesth. Anal.* 62:920–24
31. Romagnoli, A., Keats, A. S. 1975. Comparative respiratory depression of tilidine and morphine. *Clin. Pharmacol. Ther.* 17:523–28
32. Weil, J. V., McCullough, R. E., Kline, J. S., Sodal, I. E. 1975. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N. Engl. J. Med.* 292:1103–6
33. Kryger, M. H., Yacoub, O., Dosman, J., Macklein, P. T., Anthonisen, N. R. 1976. Effect of meperidine on occlusion pressure responses to hypercapnia and hypoxia with and without external inspiratory resistance. *Ann. Rev. Resp. Dis.* 114:333–40
34. Bellville, J. W., Escarraga, L. A., Wallenstein, S. L., Houde, R. W. 1968. The respiratory effect of codeine and morphine in man. *Clin. Pharmacol. Ther.* 9:435–41
35. Bellville, J. W., Seed, J. C. 1968. A comparison of the respiratory depressant effects of dextropropoxyphene and codeine in man. *Clin. Pharmacol. Ther.* 9:428–34
36. Harper, M. H., Hickey, R. F., Cromwell, T. H., Linwood, S. 1976. The magnitude and duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man. *J. Pharmacol. Exp. Ther.* 199:464–68
37. McClain, D. A., Hug, C. C. 1980. Intravenous fentanyl kinetics. *Clin. Pharmacol. Ther.* 28:106–14
38. Stoeckel, H., Schuttler, J., Magnussen, H., Hengstmann, J. H. 1982. Plasma fentanyl concentrations and the occurrence of respiratory depression in volunteers. *Br. J. Anaesth.* 54:1087–95
39. Stoeckel, H., Hengstmann, J. H., Schuttler, J. 1979. Pharmacokinetics of fentanyl as a possible explanation for recurrence of respiratory depression. *Br. J. Anaesth.* 51:741–45
40. Adams, A. P., Pybus, D. A. 1978. Delayed respiratory depression after use of fentanyl during anesthesia. *Br. Med. J.* 1:278–79
41. Becker, L. D., Paulson, B. A., Miller, R. D., Severinghaus, J. W., Eger, E. I. 1976. Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone

used to supplement nitrous oxide anesthesia. *Anesthesiology* 44:291–96
42. Cartwright, P., Prys-Roberts, C., Gill, K., Dye, A., Stafford, M., Gray, A. 1983. Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. *Anesth. Anal.* 62:966–74
43. Meuldermans, W. E. G., Herkmans, R. M. A., Heykants, J. J. P. 1982. Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. *Arch. Int. Pharmacodyn. Ther.* 257:4–19
44. Romagnoli, A., Keats, A. S. 1980. Ceiling effect for respiratory depression by nalbuphine. *Clin. Pharmacol. Ther.* 27:478–85
45. Nagashima, H., Karamanian, A., Malovany, R., Radnay, P., Aug, M., Koerner, S., Foldes, F. F. 1976. Respiratory and circulatory effects of intravenous butorphanol and morphine. *Clin. Pharmacol. Ther.* 19:738–45
46. Heel, R. C., Brogden, R. N., Speight, T. M., Avery, G. S. 1979. Buprenorphine: A review of its pharmacological properties and therapeutic efficacy. *Drugs* 17:81–110
47. Romagnoli, A., Keats, A. S. 1984. Ceiling respiratory depression by dezocine. *Clin. Pharmacol. Ther.* 35:367–73
48. Snyder, S. S. 1984. Drug and neurotransmitter receptors in the brain. *Science* 224:22–31
49. Jones, J. G. 1983. The respiratory effects of meptazinol. *Postgrad. Med. J.* 59(Suppl. 1):72–77
50. Keats, A. S., Telford, J. 1966. Studies of analgesic drugs: X respiratory effects of narcotic antagonists. *J. Pharmacol. Exp. Ther.* 151:126–32
51. Murphy, M. R., Hug, C. C. 1982. The enflurane sparing effect of morphine, butorphanol and nalbuphine. *Anesthesiology* 57:489–92
52. Hoffman, J. C., DiFazio, C. A. 1970. The anesthesia sparing effect of pentazocine, meperidine and morphine. *Arch. Int. Pharmacodyn. Ther.* 186:261–68
53. Bellville, J. W., Fleischle, G. 1968. The interaction of morphine and nalorphine on respiration. *Clin. Pharmacol. Ther.* 9:152–61
54. Rouge, J. C., Banner, M. P., Smith, T. C. 1969. Interactions of levallorphan and meperidine. Failure to find antagonism after clinical doses. *Clin. Pharmacol. Ther.* 10:643–54
55. Kallos, T., Hudson, H. E., Rouge, J. C., Smith, T. C. 1972. Interaction of the effects of naloxone and oxymorphone on human respiration. *Anesthesiology* 36: 278–85
56. Prough, D. S., Roy, R., Bumgarner, J., Shannon, G. 1984. Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. *Anesthesiology* 60:485–86
57. Andree, R. A. 1980. Sudden death following naloxone administration. *Anesth. Anal.* 59:782–84
58. Gasser, J. C., Kaufman, R. D., Bellville, J. W. 1975. Respiratory effects of lorazepam, pentobarbital and pentazocine. *Clin. Pharmacol. Ther.* 18:170–74
59. Stephen, G. W., Banner, M. P., Wollman, H., Smith, T. C. 1969. Respiratory pharmacology of mixtures of scopolamine with secobarbital and with fentanyl. *Anesthesiology* 31:237–42
60. Harris, E. A., Slawson, K. B. 1965. The respiratory effects of therapeutic doses of cyclobarbitone, triclofos, and ethchlorvynol. *Br. J. Pharmacol.* 24:214–22
61. Hirshman, C. A., McCullough, R. E., Cohen, P. J., Weil, J. V. 1975. Effect of pentobarbitone on hypoxic ventilatory drive in man. *Br. J. Anaesth.* 47:963–68
62. Aldrete, J. A., Itkin, I. H. 1969. Effects of chloral hydrate on the respiration of non-asthmatic and asthmatic patients. *J. Allergy* 42:342–48
63. Gasser, J. C., Bellville, J. W. 1976. The respiratory effects of hydroxyzine, diazepam and pentazocine in man. *Anaesthesia* 31:718–23
64. Steen, S. N., Amaha, K., Weitzner, S. W., Martinez, L. R. 1967. The effect of chlordiazepoxide and pethidine alone and in combination on the respiratory response to carbon dioxide. *Br. J. Anaesth.* 39:459–63
65. Paulson, B. A., Way, W. L. 1983. The effects of intravenous lorazepam alone and with meperidine on ventilation in man. *Acta Anesthesiol. Scand.* 27:400–2
66. Longbottom, R. T., Pleuvry, B. J. 1984. Respiratory and sedative effects of triazolam in volunteers. *Br. J. Anaesth.* 56:179–85
67. Pleuvry, B. J., Maddison, S. E., Odeh, R. B., Dodson, M. E. 1980. Respiratory and psychological effects of oral temazepam in volunteers. *Br. J. Anaesth.* 52:901–6
68. Geddes, D. M., Rudolf, M., Saunders, K. B. 1976. Effect of nitrazepam and flurazepam on the ventilatory response to carbon dioxide. *Thorax* 31:548–51
69. Rudolf, M., Geddes, D. M., Turner, J. A. M., Saunders, K. B. 1978. Depression of central respiratory drive by nitrazepam. *Thorax* 33:97–100

70. Lambertsen, C. J., Wendel, H., Longenhagen, J. B. 1961. The separate and combined respiratory effect of chloropromazine and meperidine in normal men controlled at 46 mmHg alveolar pCO_2. *J. Pharmacol. Exp. Ther.* 131:381–93
71. Keats, A. S., Telford, J., Kurosu, Y. 1961. "Potentiation" of meperidine by promethazine. *Anesthesiology* 22:34–41
72. Hoffman, J. C., Smith, T. C. 1970. The respiratory effects of meperidine and propiomazine in man. *Anesthesiology* 32:325–31
73. Mull, T. D., Smith, T. C. 1974. Comparison of the ventilatory effects of two antiemetics, benzquinamide and prochloroperazine. *Anesthesiology* 40:581–87
74. Kallos, T., Smith, T. C. 1969. The respiratory effects of innovar given for premedication. *Br. J. Anaesth.* 41:303–6
75. Welsh, M. J., Heistad, D. D., Abboud, F. M. 1978. Depression of ventilation by dopamine in man. *J. Clin. Invest.* 61:708–13
76. Bainbridge, C. W., Heistad, D. D. 1980. Effect of haloperidol on ventilatory responses to dopamine in man. *J. Pharmacol. Exp. Ther.* 213:13–17
77. Ward, D. S. 1984. Stimulation of hypoxic ventilatory drive by droperidol. *Anesth. Anal.* 63:106–10
78. Prokocimer, P., Delavault, E., Rey, F., Lefevre, P., Mazze, R. I., Desmonts, J. M. 1983. Effects of droperidol on respiratory drive in humans. *Anesthesiology* 59:113–16
79. Gasser, J. C., Bellville, J. W. 1975. Interactions of the effects of hydroxyzine and pentazocine on human respiration. *Anesthesiology* 43:599–601
80. Gabathuler, M. L., Kaufman, R. D. 1981. Respiratory depression of intravenous hydroxyzine in man; potency, duration and lack of reversal by naloxone. *Anesth. Anal.* 60:634–37
81. Bellville, J. W., Swanson, G. D., Aqleh, K. A. 1975. Respiratory effect of delta-9-tetrahydrocannabinol. *Clin. Pharmacol. Ther.* 17:541–48
82. Malit, L. A., Johnstone, R. E., Bourke, D. I., Kulp, R. A., Klein, V., Smith, T. C. 1975. Intravenous Δ-9-tetra hydrocannabinol: Effects on ventilatory control and cardiovascular dynamics. *Anesthesiology* 42:666–73
83. Johnstone, R. E., Lief, P. L., Kulp, R. A., Smith, T. C. 1975. Combination of Δ-9-tetrahydrocannabinol with oxymorphone or pentobarbital: Effects on ventilatory control and cardiovascular dynamics. *Anesthesiology* 42:674–84
84. Gross, J. B., Caldwell, C. B., Shaw, L. M., Laucks, S. O. 1983. The effect of lidocaine on the ventilatory response to carbon dioxide. *Anesthesiology* 59:521–25
85. Lam, A. M., Clement, J. L. 1984. Effect of cimetidine premedication on morphine-induced ventilatory depression. *Can. Anaesth. Soc. J.* 31:36–43
86. Gold, M. I., Reichenberg, S., Freeman, E. 1969. Respiratory depression in the sedated bronchitic patient: Rapid version of the CO_2 response curve. *Anesthesiology* 30:492–99
87. Forrest, W. H., Bellville, J. W. 1964. The effect of sleep plus morphine on the respiratory response to carbon dioxide. *Anesthesiology* 25:137–41
88. Delpierre, S., Jammes, Y., Grimaud, C., Dugue, P., Arnaud, A., Charpin, J. 1981. Influence of anxiolytic drugs (prazepam and diazepam) on respiratory center output and CO_2 chemosensitivity in patients with lung diseases. *Respiration* 42:15–20
89. Martin, R., Lamarche, Y., Tetrault, J. P. 1983. Epidural and intrathecal narcotics. *Can. Anaesth. Soc. J.* 30:662–73
90. Kafer, E. R., Brown, J. T., Scott, D., Findlay, J. W. A., Butz, R. F., et al. 1983. Biphasic depression of ventilatory responses to CO_2 following epidural morphine. *Anesthesiology* 58:418–27
91. Camporesi, E. M., Nielsen, C. H., Bromage, P. R., Durant, P. A. C. 1983. Ventilatory CO_2 sensitivity after intravenous and epidural morphine in volunteers. *Anesth. Anal.* 62:633–40
92. Rawal, N., Wattwil, M. 1984. Respiratory depression after epidural morphine—An experimental and clinical study. *Anesth. Anal.* 63:8–14
93. Moore, A., Bullingham, R., McQuay, H., Allen, M., Baldwin, D., Cole, A. 1984. Spinal fluid kinetics of morphine and heroin. *Clin. Pharmacol. Ther.* 35:40–45
94. Kalia, P. K., Madan, R., Saksena, R., Batra, R. K., Gode, G. R. 1983. Epidural pentazocine for postoperative pain relief. *Anesth. Anal.* 62:949–50
95. Rigg, J. R. A., Ilsley, A. H., Vedig, A. E. 1981. Relationship of ventilatory depression to steady-state blood pethidine concentrations. *Br. J. Anaesth.* 53:613–20
96. Calverley, P. M. A., Robson, R. H., Wraith, P. K., Prescott, L. F., Flenley, D. C. 1983. The ventilatory effects of doxapram in normal man. *Clin. Sci.* 65:65–69
97. Papadopoulos, C. N., Keats, A. S. 1962.

Specific and nonspecific antagonism of morphine-induced respiratory depression. *Anesthesiology* 23:86–91
98. Bellville, J. W. 1964. Interaction of caffeine and morphine on respiration. *J. Pharmacol. Exp. Ther.* 143:165–68
99. Bourke, D. L., Allen, P. D., Rosenberg, M., Mendes, R. W., Karabelas, A. N. 1983. Dextroamphetamine with morphine: Respiratory effects. *J. Clin. Pharmacol.* 23:65–70
100. Snir-Mor, I., Weinstock, M., Davidson, J. T., Bahar, M. 1983. Physostigmine antagonizes morphine-induced respiratory depression. *Anesthesiology* 59:6–9
101. Stroud, M. W., Lambertsen, C. J., Ewing, J. H., Kough, R. H., Gould, R. A., Schmidt, C. F. 1955. The effects of aminophylline and meperidine alone and in combination on the respiratory response to carbon dioxide inhalation. *J. Pharmacol. Exp. Ther.* 114:461–69