Standard Clinical Indicators of Opioid Induced Respiratory Depression (OIRD) Do Not Consistently Detect Opioid Toxicity that is Manifest as Ataxic Breathing

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Background: The drive to breathe with a regular rhythm and pattern depends upon a complex and widely distributed state-dependent neuronal system in the brainstem in which μ-opioid receptors are embedded. Consequently, coupling of opioids with pain and respiratory neurons inhibits all aspects of respiratory control. Inhibition of opioid-sensitive neurons in the pre-Bötzinger complex, the putative respiratory pattern generator, alters both the rhythm and rate of breaths. Although irregular or ataxic breathing is a well-recognized sign of opioid induced respiratory depression (OIRD), the commonly monitored signs of bradypnea, hypoxemia and sedation do not directly assess the degree of ataxic breathing. There is evidence that regular or ataxic breathing may be a sensitive indicator of OIRD, occurring before other toxic effects such as bradypnea and sedation. We hypothesized that ataxic breathing would be evident when traditional measures of opioid toxicity such as bradypnea and altered mental alertness were not present.

Methods: With institutional review board approval and informed consent, 26 healthy volunteers received remifentanil and propofol to emulate the respiratory depression observed during postoperative pain therapy and sleep. All volunteers received 2 lpm of oxygen to prevent desaturation. Respiratory variables were collected from respiratory inductance plethysmography (RIP) bands sampled at 100 Hz. For each of the steady state drug administration periods, respiratory rate was calculated minute by minute, mental status was determined by the Modified Observer's Assessment of Alertness and Sedation (MOAA/S), and an automated machine learning classifier scored the ataxic breathing severity on a scale of 0-4 (4 = worst ataxia; 0 = no ataxia). Clinically significant bradypnea was defined as RR < 9 breaths/min, reduced mental alertness as MOAA/S score of < 4, and significant ataxic breathing as category ≥ 2.

Results: Significant ataxic breathing (category ≥ 2) was present in 53.2% of subjects when there was high mental alertness (MOAA/S score of ≥ 4) and there was no significant reduction of respiratory rate (RR 8-10). See Figure and Table for details in each respiratory rate range.

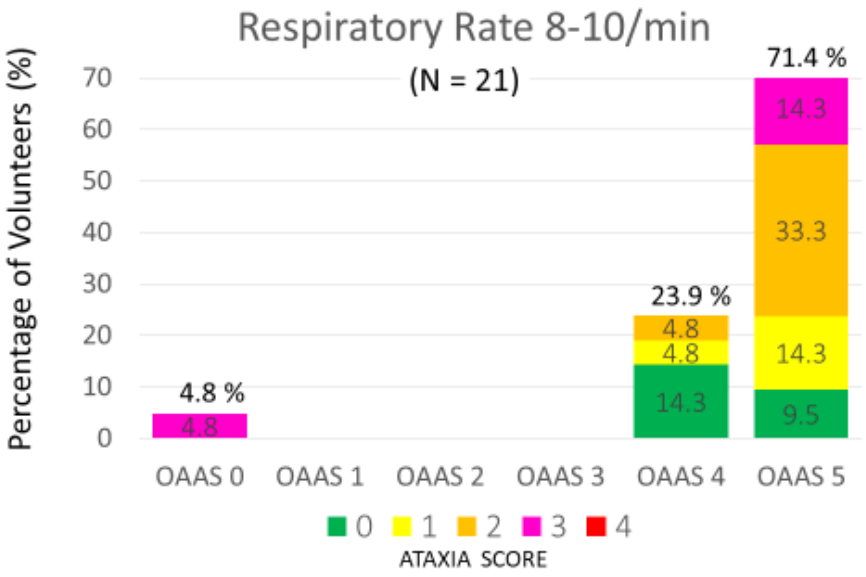

Figure: Percentage of volunteers observed to have ataxic breathing when the toxic effects of opioids were not evident for the traditional measures of respiratory rate or alertness.

	RR 0-4/min (n=50)					RR 5-7/min (n=36)					RR > 10/min (n=14)				
MOAA/S	Ataxia 0	Ataxia 1	Ataxia 2	Ataxia 3	Ataxia 4	Ataxia 0	Ataxia 1	Ataxia 2	Ataxia 3	Ataxia 4	Ataxia 0	Ataxia 1	Ataxia 2	Ataxia 3	Ataxia 4
0	-	-	2	8	12	-	2.8	-	-	2.8	-	-	-	-	-
1	-	-	2	2	20	-	-	-	11.4	2.8	-	-	-	-	-
2	2	-	4	2	6	-	2.8	-	5.6	-	21.4	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	-	4	24	-	-	2.8	-	5.6	14.3	7.1	-	-	-
5	-	-	2	4	6	2.8	7.8	22.2	27.8	2.8	35.7	14.3	7.1	-	-

Table: Percentage of volunteers at each ataxic breathing category for other respiratory rate ranges.

Conclusions: Ataxic breathing may be present without sedation or clinically significant bradypnea. Ataxic breathing is a sensitive indicator of OIRD and can be used in conjunction with standard clinical indicators to detect opioid induced respiratory depression.