

Emergency Admissions of Opioid Drug Abusers for Overdose: A Chronobiological Study of Enhanced Risk

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Study objective: To determine whether there is a specific temporal risk for opioid drug overdose.

Design: To study patients presenting to the ED in a comatose state from accidental drug opioid overdose.

Participants: Two hundred seventy-four patients were admitted to the ED of the Hospital of Ferrara, Italy, from 1988 to 1990, 225 men (82.1%; mean age, 25±3.4 years) and 49 women (17.9%; mean age, 23.5±2.8 years).

Interventions: Month, day, and hour and minute of admissions were recorded, and time-qualified frequency data were analyzed by the single cosinor method.

Results: Cosinor analysis demonstrated a significant circadian rhythm for both the total number of observations and the separate male and female subgroups with an early evening peak ("acrophase") at about 7:00 PM. No significant circannual rhythm was evident, but for the total group a significant 6-month rhythm was demonstrable with peaks in late November and late May.

Conclusion: There is a distinct "chronorisk" of opioid drug overdose in the early evening hours.

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INTRODUCTION

Drug overdose is a frequent and real emergency, the outcome of which depends on timely, specific intervention. Any clue to the increased likelihood of a given event can heighten suspicion and shorten the time to effective action.

The concept of "chronorisk"¹ involves identification of a greater risk of morbidity or mortality that recurs in relation to cyclic changes in environmental or biological rhythms.

Once the periodicity of the cyclic change is known, the event becomes to some extent predictable. Significant circadian or circannual rhythms have been recognized in relation to acute myocardial infarction,² sudden cardiac death,³ fatal pulmonary embolism,⁴ and stroke.⁵

MATERIALS AND METHODS

We conducted a prospective study of all patients comatose from accidental drug overdose who were admitted to our emergency department from January 1, 1988, through December 31, 1990. Drug overdose patients who were not in a coma were excluded. The diagnosis was clinical, historical (from witnesses or after patient recovery), physical (miosis, stigmata of drug abuse), or course (response to naloxone). It was not possible to confirm the presumptive diagnosis by means of specific toxicologic assays. The 274 subjects included 225 men (82.1%; mean age, 25±3.4 years) and 49 women (17.9%; mean age, 23.5±2.8 years). Resuscitation was successful in all but five cases. The majority of the patients (187, 68.2%) admitted IV abuse of heroin, with two or more fixes daily.

The month, day, and hour and minute of each admission were tabulated covering the 24-hour or 12-month span, and the numeric frequency of the events was computed for each hour of the day and each month of the year. For circadian calculations, admissions were categorized into 24 1-hour increments, eg, 6:00 AM to 6:59 AM reported as 6:00 AM. We used the time of patients' presentation to the ED and not the time the overdose took place due to the peculiar organization of emergency services in Ferrara. The S

Figure 1.

Definition of chronobiologic terms.

Cosinor is a statistical summary that displays polar coordinates of rhythm characteristics. The single cosinor adjusts, by least squares, a rhythmic function with a presumed period to a data series, thus providing point-and-interval estimates of mesor, amplitude, and acrophase.

Mesor is an acronym for the midline-estimating statistic of rhythm. Rhythm-adjusted mean is defined as the average values of rhythmic function fitted to the data. The mesor differs from the arithmetic mean whenever the data are nonequidistant and/or cover a nonintegral number of cycles. In this case, the mesor is usually more accurate (ie, associated with less bias from sampling). When data are equidistant, the mesor also is usually more precise (ie, associated with a smaller standard error) if the times series undergoes a rhythmic change.

Acrophase is a lag from a given reference time (such as midnight) of the rhythm's crest time, defined by the rhythmic function fitted to the data. The acrophase is expressed in (negative) degrees, with 360° equated to the period length and 0° taken as the reference time. In circadian analysis, the 0° is chosen at midnight, and the acrophase can also be expressed in hours and minutes. In circannual analysis, the 0° is set at December 22.

Amplitude is half of the total predictable change in a rhythm, represented by the distance from Mesor to the peak or through cosine curve best fitting the data.

Circadian rhythm is a rhythm of approximately 24 hours.

Circannual rhythm is a rhythm of approximately 1 year.

Table.

Circadian and circannual periodicity in overdose emergency admissions.

	Circadian Rhythm						
	Period (h)	%R*	Mesor ± SE	Amplitude ± SE	Acrophase (PM)	95% Confidence Limits	P
Total	24	78.1	11.42±0.94	11.57±1.33	7:03	17.52, 20.14	<.001
Women	24	43.1	2.04±0.29	1.62±0.41	7:24	16.39, 22.09	.003
Men	24	78.2	9.37±0.81	9.95±1.15	7:00	17.49, 20.10	<.001
	Circannual Rhythm						
	Period (mo)	%R*	Mesor ± SE	Amplitude ± SE	Acrophase (°)	95% Confidence Limits	P
Total	6	51.6	23.00±1.82	7.97±2.57	-310.4	-240.0, -20.9	.038
Women	6	42.6	4.08±0.41	1.48±0.57	-343.0	—	NS
Men	6	46.8	18.92±1.70	6.76±2.41	-303.7	—	NS

*Mean of percentage reduction in standard error of mesor versus that of arithmetic mean.

Anna hospital is responsible for response and transport of all out-of-hospital medical emergencies within the city limits and suburban area (population, approximately 200,000). The average time from receipt of a call to arrival in the ED from anywhere in the city is 5 to 10 minutes.

The time-qualified frequency series were analyzed by means of the single cosinor method.⁶ Three parameters characterize this model: mesor, amplitude, and acrophase (see Figure 1 for definitions).

The statistical significance of cosine function is detected by the percentage of rhythm as a ratio of the variance of the fitted model and the variance of raw data made equal to 100%. Significance levels were $P < .05$. A bivariate statistical confidence region was computed with at least 95% probability of containing the actual amplitude and acrophase of the rhythm (95% confidence limits).

RESULTS

Results of cosinor analysis for all cases and after stratification by sex are summarized in the Table and represented in Figure 2. A statistically significant circadian rhythm was shown for all cases ($P < .001$), men ($P < .001$), and women ($P = .003$). No circannual rhythmicity was evident. A 6-month rhythm with peaks in late November and late May (acrophase at -310.4° and -130.4° , respectively; $P = .038$) was found for the total group but not for sex subgroups.

DISCUSSION

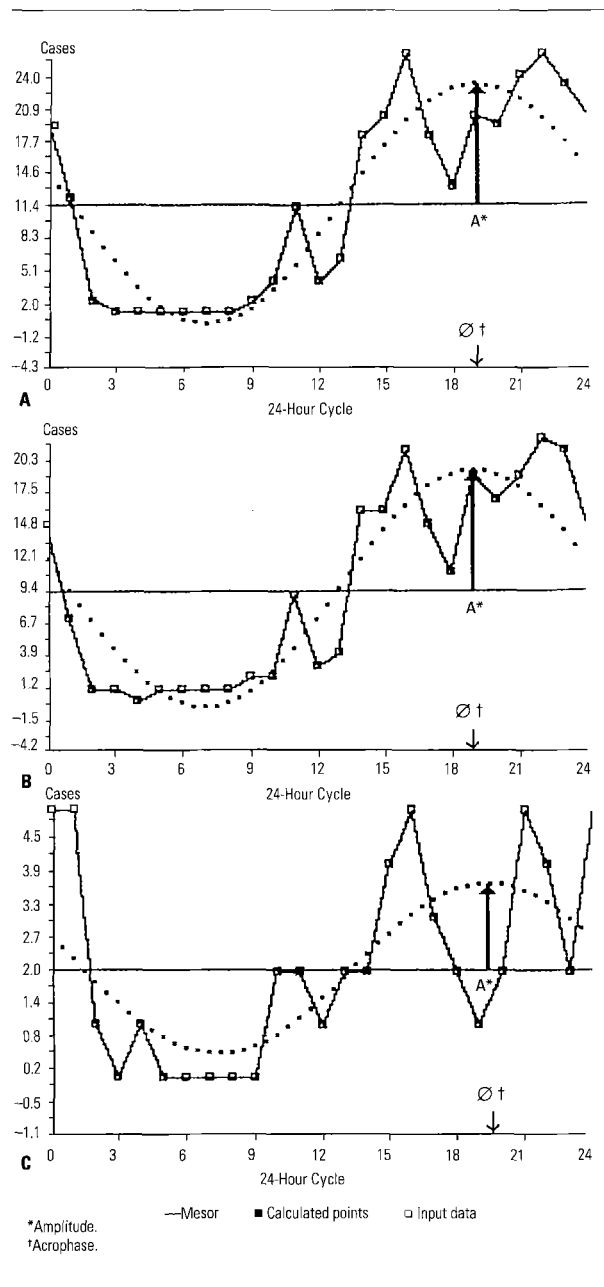
These results are consistent with those reported by Morris,⁷ who found significant acrophases for total admissions, men, and women at 6:17 PM, 6:23 PM, and 6:18 PM, respectively. Morris' data fall well within the 95% confidence limits of our study (Table) and give firm support to the existence of an early-evening chronorisk for opioid drug overdose admissions to the ED. Morris' circannual data (peaks in late July, late May, and early August) are at variance with ours. Study of geographic, ethnic, and societal differences between Chicago and Ferrara may provide the explanation.

Nevertheless, it is somewhat difficult to explain why opioid abusers present to the ED at a preferential time despite continuing, iterative self-administration. Hours of work and the constraints of staying employed are obvious considerations,⁷ even if a different circadian susceptibility to various drugs can be hypothesized.⁸

CONCLUSION

Although the specific biological and societal mediators of the cycle are unknown, emergency physicians can put to

Figure 2. Circadian rhythm of emergency admissions of drug abusers for overdose. Representation on cartesian axes is for (A) all cases, (B) men, and (C) women.



practical use the recognition of a clearly identified chronorisk for drug overdose in the early evening hours.

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CORRECTION

in "Safety and Efficacy of Rectal Prochlorperazine for the Treatment of Migraine in the Emergency Department" (*Ann Emerg Med* August 1994;24:237-241), the figure key was printed incorrectly. The corrected figure is reproduced below.

