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Diurnal variation in probability of death following self-poisoning in Sri Lanka—evidence for chronotoxicity in humans

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Background The absorption, distribution, metabolism and elimination of medicines are partly controlled by transporters and enzymes with diurnal variation in expression. Dose timing may be important for maximizing therapeutic and minimizing adverse effects. However, outcome data for such an effect in humans are sparse, and chronotherapeutics is consequently less practised. We examined a large prospective Sri Lankan cohort of patients with acute poisoning to seek evidence of diurnal variation in the probability of survival.

Methods In all, 14 840 patients admitted to hospital after yellow oleander (*Cascabela thevetia*) seed or pesticide [organophosphorus (OP), carbamate, paraquat, glyphosate] self-poisoning were investigated for variation in survival according to time of ingestion.

Results We found strong evidence that the outcome of oleander poisoning was associated with time of ingestion ($P < 0.001$). There was weaker evidence for OP insecticides ($P = 0.041$) and no evidence of diurnal variation in the outcome for carbamate, glyphosate and paraquat pesticides. Compared with ingestion in the late morning, and with confounding by age, sex, time of and delay to hospital presentation and year of admission controlled, case fatality of oleander poisoning was over 50% lower following evening ingestion (risk ratio = 0.40, 95% confidence interval 0.26–0.62). Variation in dose across the day was not responsible.

Conclusions We have shown for the first time that timing of poison ingestion affects survival in humans. This evidence for chronotoxicity suggests chronotherapeutics should be given greater attention in drug development and clinical practice.

Keywords Circadian rhythm, self-injurious behaviour, toxicology, poisoning, *Cascabela thevetia*, pesticides, Sri Lanka

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Introduction

The circadian clock influences a large number of rhythms in physiology, behaviour and disease.[1] Diseases with circadian rhythms include asthma, arthritis, cancer, depression, myocardial infarction, hypertension and peptic ulcer disease[1]; treatment at particular times of day may therefore be more effective.[2–4] The effectiveness and toxicity of pharmaceuticals also vary according to the time of administration, owing to variation in pharmacokinetics and dynamics.[1,5] For example, administration of oxaliplatin, 5-FU and folinic acid, according to their circadian rhythm, for metastatic colorectal cancer resulted in less toxicity and increased response rate in one clinical trial.[6] Simvastatin, a hypolipidaemic drug, is administered at 22:00 to increase inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity.[7]

Absorption may be affected by variation in transporter activity; rodent studies have indicated peak P-glycoprotein activity in intestine and liver at the end of the simulated daylight phase.[8,9] Drug metabolism may be affected by rhythms in liver blood flow (increased in the morning)[10] and liver enzyme activity: cytochrome p450 (CYP450) activity is increased in both rodents and humans at the end of the light phase.[11,12] However, chronotherapeutics is not widely practised, and the majority of drugs are administered without regard to relevant circadian rhythms. One reason may be the paucity of hard outcome data in humans to support the approach and stimulate research.

Large cohorts of poisoned patients offer the opportunity to address the importance of drug administration timing because hard outcomes are relatively common in this group of patients and time of self-administration highly variable. Mouse studies have indicated that chronotoxicity does occur: in one study, paracetamol (acetaminophen) toxicity was higher at 21:00 (100% mortality) compared with 09:00 (30% mortality) following injection of 600 mg/kg.[13] These results correlated with high Cytochrome P450 2E1 (CYP2E1) activity and low liver glutathione content at 21:00 compared with 09:00; of note, mice are nocturnal animals, so the rodent circadian cycle of activity and feeding is 12 h out of phase compared with the human cycle.

Self-poisoning is a major clinical problem in rural Asia, killing at least 300 000 people every year, the majority following ingestion of pesticides or plants.[14,15] Medical management is difficult, with case fatality often around 10%. Pesticide poisoning is now recognized as the single most important global cause of suicide.[16] In 2002, we set up a prospective study of patients admitted to two referral hospitals in north central Sri Lanka with which to study the natural history and treatment of pesticides and yellow oleander (*Cascabela thevetia*) seed poisoning.[17]

To determine whether chronotoxicity occurs in humans, we studied the importance of poison ingestion time on mortality in this large cohort. We hypothesized that case fatality would fluctuate over the course of a day in line with circadian fluctuations in transporters and CYP450s. More specifically, in the evening, increased P-glycoprotein activity—reducing absorption—would decrease fatality from oleander ingestion, but not pesticides, whereas increased CYP450 activity in the evening—increasing activation—would increase fatality in organophosphorus (OP) insecticide poisoning but not oleander poisoning.

Methods

Data collection

The current analysis was based on a large cohort of patients admitted to hospital for self-poisoning in Sri Lanka between March 2002 and December 2009.[17,18] The stated time of poison ingestion was recorded for the majority; this permitted the investigation of periodic variation in the case fatality of the five most commonly ingested poisons.

A total of 29 894 records of self-poisoning were available; 28% were recorded as 'pesticide unknown', 'other pesticide' or 'unknown' and were not further analysed. Of the remaining records, 14 840 involved ingestion of a single poison, i.e. yellow oleander (*C. thevetia*) seeds, OP or carbamate insecticide, paraquat or glyphosate, and were included for further analysis. We did not include pharmaceuticals in the analysis because deaths were very uncommon with these compounds.

Statistical analysis

Defining five groups according to the poison ingested, differences between groups in demographic and clinical measures were assessed using a non-parametric test of medians across groups (year of admission, time to presentation, concentration of poison ingested), chi-squared tests (gender, case-fatality) or ordinary least squares regression (age).

To investigate diurnal variation in survival across poisons, periodic logistic regression was used.[19] The effect of time of ingestion on the odds of case fatality for each poison in turn was estimated as the amplitudes and frequencies of two sine and two cosine terms combined in a linear model. This procedure allowed a statistically powerful analysis of the periodic fluctuations in mortality over the course of a day. To aid interpretation, each model was presented graphically, and, using Poisson regression, the risk ratios of death associated with each of five 4-h periods were estimated using the morning period (08:00–12:00) as a reference.

Analyses were adjusted for age and sex of patients admitted and year of admission. Further adjustment for time of admission was also performed to control confounding by variations in clinical management over the course of the day. The impact of elapsed

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time from poison ingestion to admission was also controlled for when assessing any diurnal variation in case fatality. Information on the dose ingested was only consistently recorded for oleander self-poisoning episodes; therefore, a further sensitivity analysis additionally controlled for confounding by the number of seeds ingested for oleander poisoning.

All analyses assumed that any daily fluctuations in mortality were consistent throughout the study period analysed. Statistical analyses were performed using Stata version 11 (Stata Corp, College Station, TX, USA, 2009).

Results

Cases

During 2002–09, 14 840 patients were admitted for self-poisoning with oleander, OP or carbamate insecticide, paraquat or glyphosate. Of these, 372 (2.51%) admissions did not have a time of poison ingestion recorded and were excluded from subsequent analysis.

The number of cases with each poison varied considerably (Table 1). Oleander was the most common poison ingested, followed by OP insecticides, glyphosate, carbamates and paraquat. There was evidence of an association between poison and year of admission ($P < 0.001$), with OP insecticide cases becoming the most common poison ingested in later years of the study. The total number of cases reported each year was in part a reflection of the number of participating hospitals. Males represented a greater proportion of the cohort (61%) compared with females, although the ratio of males to females varied across the poisons (Table 1; $P < 0.001$). The median age of patients was 25 (Interquartile range (IQR) 19–36) years. The median age at admission varied by poison ($P < 0.001$), with those ingesting oleander being younger on average (Table 1). There was strong evidence against equal case fatality across the five different poisons ($P < 0.001$), with paraquat associated with the highest case fatality (44.2%) followed by OP insecticides (11.1%). Year on year reductions in case fatality were particularly apparent for paraquat.

The incidence of poison ingestion varied by time of day (Figure 1). Poisons were most commonly reported to have been ingested during the late afternoon and evening. The frequency of poison ingestion decreased from 21:00 onwards in all poisons, with considerably fewer cases reporting ingestion between midnight and 06:00. Digit preference was apparent in the reported ingestion times: large numbers of patients reported ingestion times on the hour or half past the hour, but very few reported ingestion outside of these times. However, this rounding of reported ingestion time to the nearest hour or half-hour occurred throughout the day; therefore, estimated associations should be subject to a mild attenuation at most.

A number of contextual variables that may influence case fatality were reviewed, including the time between ingestion and hospital presentation, dose of poison ingested and medical treatment. Across all poisons, time to presentation appeared shortest when poison ingestion occurred in the afternoon or evening (median 5.01 h) and longest between midnight and 04:00 (median 7.14 h; $P < 0.001$). Only patients who ingested oleander had consistently recorded (87% complete) information regarding the dose of poison ingested. The median number of oleander seeds ingested (three seeds) did not vary at different times of the day ($P = 0.79$). Medical records review indicated that 451 (8.1%) patients were fitted with a temporary pacemaker after ingesting the cardiotoxic oleander seeds. There was no statistical evidence ($P = 0.16$; Kruskal–Wallis test of equal distributions) of an association between time of ingestion and the time until referral for a pacemaker among the subgroup of patients ($n = 280$) referred within 24 h—this is the group for whom any diurnal variation in access to treatment would be most apparent. Further details of these data are available from the authors.

Case fatality by reported time of ingestion

There was strong evidence of diurnal variation in the probability of death from oleander self-poisoning ($P < 0.001$; Table 2 and Figure 2) using periodic regression analysis; this trend remained after adjustment for age, sex, time until presentation, time of admission and year of admission ($P < 0.001$; Table 2). There was increased case fatality after morning ingestions and decreased case fatality after ingestions in the afternoon and evening (Figure 2 and Table 2). A sensitivity analysis based on those patients with dose data available ($n = 4889$) was performed. The risk ratio for case fatality comparing poison ingestion at 16:00–20:00 with 08:00–12:00 was 0.44 [95% confidence interval (CI): 0.28–0.70]; this same association was observed when controlling for the number of seeds ingested (Risk Ratio (RR) = 0.46, 95% CI: 0.29–0.73).

There was also evidence of diurnal variation in case fatality following OP insecticide self-poisoning ($P = 0.002$; Table 2); this evidence became weaker with adjustment for age, sex, time of admission, year of admission and time to presentation ($P = 0.041$; Table 2). Patients' age and sex appeared to be the most important variables contributing to the attenuation. However, in contrast to oleander poisoning, the probability of death after OP insecticide ingestion appeared increased in the afternoon and evening (Figure 2 and Table 2).

There are many different OP insecticides, with differing requirements for activation by CYP450s[20] and interactions with transporters, which might have hidden an effect for individual OPs. We therefore looked at diurnal variation in the case fatality for the two commonest OP insecticides: chlorpyrifos

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Table 1 Descriptive characteristics of admissions for deliberate self-harm by poison of ingestion, Sri Lanka, 2002–09

	Oleander		Organophosphate		Glyphosate		Carbamate		Paraquat	
	Dead/total (%)	Row %[a]	Dead/total (%)	Row %[a]	Dead/total (%)	Row %[a]	Dead/total (%)	Row %[a]	Dead/total (%)	Row %[a]
Admission per year (%)[a]										
2002	45/666 (6.8)	53.0	53/397 (13.4)	31.6	3/42 (7.1)	3.3	6/82 (7.3)	6.5	37/69 (53.6)	5.5
2003	32/826 (3.9)	54.3	51/453 (11.3)	29.8	2/62 (3.2)	4.1	5/124 (4.0)	8.2	37/56 (66.1)	3.7
2004	26/805 (3.2)	46.3	96/602 (15.9)	34.6	5/99 (5.1)	5.7	10/141 (7.1)	8.1	50/91 (54.9)	5.2
2005	24/759 (3.2)	39.2	67/749 (8.9)	38.6	3/146 (2.1)	7.5	8/178 (4.5)	9.2	44/106 (41.5)	5.5
2006	28/785 (3.6)	39.0	64/753 (8.5)	37.4	5/175 (2.9)	8.7	15/190 (7.9)	9.4	49/111 (44.1)	5.5
2007	40/855 (4.7)	32.0	116/893 (13.0)	33.5	10/396 (2.5)	14.8	13/280 (4.6)	10.5	115/244 (47.1)	9.1
2008	10/542 (1.8)	24.9	89/865 (10.3)	39.7	5/304 (1.6)	14.0	11/268 (4.1)	12.3	68/198 (34.3)	9.1
2009	7/358 (2.0)	24.1	44/514 (8.6)	34.5	4/275 (1.5)	18.5	7/170 (4.1)	11.4	62/171 (36.3)	11.5
Gender (%)										
Female	93/2854 (3.3)	49.8	86/1498 (5.7)	26.1	2/554 (0.4)	9.7	19/530 (3.6)	9.2	117/299 (39.1)	5.2
Male	119/2742 (4.3)	30.2	494/3731 (13.2)	41.1	35/945 (3.7)	10.4	56/903 (6.2)	10.0	345/747 (46.2)	8.2
Age (years) (%)										
<14	8/290 (2.8)	59.2	2/112 (1.8)	22.9	0/32 (0.0)	6.5	2/40 (5.0)	8.2	2/16 (12.5)	3.3
15–24	98/3309 (3.0)	50.9	64/1650 (3.9)	25.4	5/629 (0.8)	9.7	20/498 (4.0)	7.7	165/415 (39.8)	6.4
25–44	73/1686 (4.3)	29.0	219/2396 (9.1)	41.2	11/644 (1.7)	11.1	26/630 (4.1)	10.8	207/454 (45.6)	7.8
45–64	25/269 (9.3)	15.5	220/913 (24.1)	52.6	15/166 (9.0)	9.6	24/248 (9.7)	14.3	76/140 (54.3)	8.1
65+	8/42 (19.0)	15.8	75/158 (47.5)	59.4	6/28 (21.4)	10.5	3/17 (17.6)	6.4	12/21 (57.1)	7.9
Total admissions (%)	212/5596 (3.8)	37.8	580/5226 (11.1)	35.3	37/1499 (2.5)	10.1	75/1433 (5.2)	9.7	462/1046 (44.2)	7.1

[a]The percentage of all poisonings in this subgroup accounted for by this particular poison.

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($n = 1863$) and dimethoate ($n = 1045$), both of which require activation by CYP450s. Little diurnal variation in case fatality was apparent for chlorpyrifos (Figure 3; $P = 0.79$), and although the time of peak case fatality for dimethoate was at roughly the same time as for OP insecticides as a whole (Figure 3), the effect was consistent with chance in this subgroup of patients ($P = 0.53$; both P values adjusted for age, sex, time to presentation, time of admission and year of admission). Analysis of other less common OP insecticides revealed some evidence of diurnal variation in case fatality after fenthion ingestion ($n = 285$, Figure 3; $P = 0.052$ after adjustment for age, sex, time of admission, year of admission and time to presentation).

We found little evidence of a relationship between time of ingestion and case fatality following carbamate, paraquat or glyphosate self-poisoning ($P = 0.221$, $P = 0.076$ and $P = 0.437$, respectively, after adjustment for age, sex, time of admission, year of admission and time to presentation; Figure 4). For carbamates, lack of evidence for a trend was also the case for the two most common subtypes: carbosulfan ($n = 435$, $P = 0.117$) and carbofuran ($n = 720$, $P = 0.788$; data not shown).

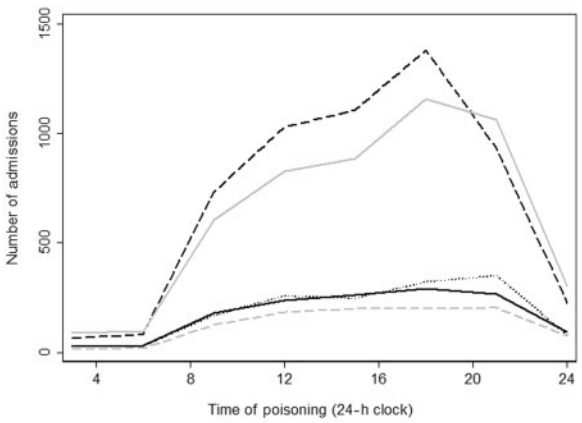

Figure 1 Number of cases with oleander (dashed back line), OP insecticide (solid grey line), carbamate (solid black line), paraquat (dashed grey line) and glyphosate (dotted black line) self-poisoning by time of ingestion

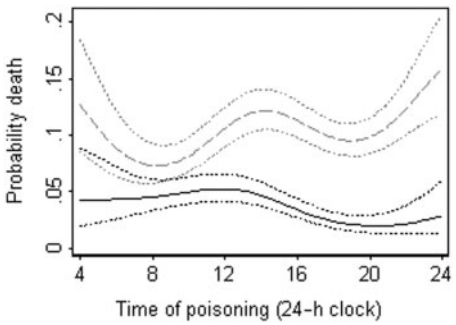

Figure 2 Diurnal variation (95% CIs) in the probability of death following oleander (solid black line) and OP insecticide (dashed grey line) ingestion

Table 2 Case fatality and risk ratios for deliberate self-poisoning with oleander and OP insecticides by ingestion time of poison, Sri Lanka, 2002–09

Poison	Time of ingestion (24 h)	Alive	Dead (%)	Unadjusted risk ratio		Adjusted[a] risk ratio	
				Risk ratio	95% CI	Risk ratio	95% CI
Oleander	0–4	61	5 (7.6)	1.37	0.55–3.39	1.03	0.39, 2.68
	4–8	289	6 (2.0)	0.37	0.16–0.85	0.40	0.17–0.92
	8–12	1229	72 (5.5)	1.00		1.00	–
	12–16	1405	67 (4.6)	0.82	0.59–1.15	0.73	0.51–1.05
	16–20	1770	44 (2.4)	0.44	0.30–0.64	0.40	0.26–0.62
	20–24	574	10 (1.7)	0.31	0.16–0.60	0.25	0.12–0.51
		Likelihood ratio test[b]		$P < 0.001$		$P < 0.001$	
OP insecticide	0–4	85	11 (11.5)	1.43	0.76–2.68	1.06	0.54–2.10
	4–8	247	31 (11.2)	1.39	0.92–2.10	1.18	0.75–1.84
	8–12	1012	88 (8.0)	1.00	–	1.00	–
	12–16	1032	135 (11.6)	1.45	1.11–1.89	1.39	1.04–1.87
	16–20	1437	161 (10.1)	1.26	0.97–1.63	1.24	0.89–1.73
	20–24	679	89 (11.6)	1.45	1.08–1.95	1.25	0.87–1.81
		Likelihood ratio test[b]		$P = 0.002$		$P = 0.041$	

[a]Model adjusted for age, sex, admission time, admission year and time to presentation.
[b]Test for evidence of diurnal variability comparing model with and without terms for diurnal variability.

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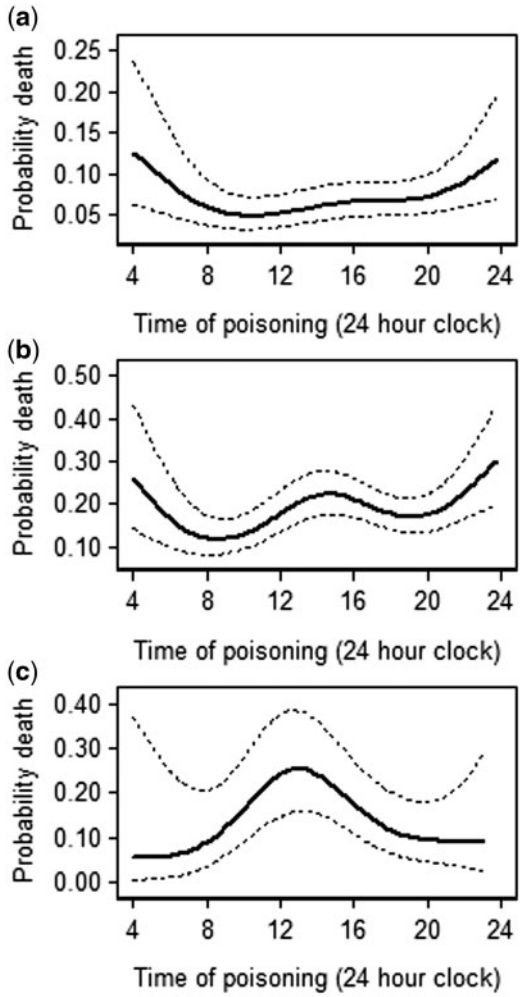

Figure 3 Diurnal variation (95% CIs) in the probability of death following (a) chlorpyrifos, (b) dimethoate or (c) fenthion ingestion

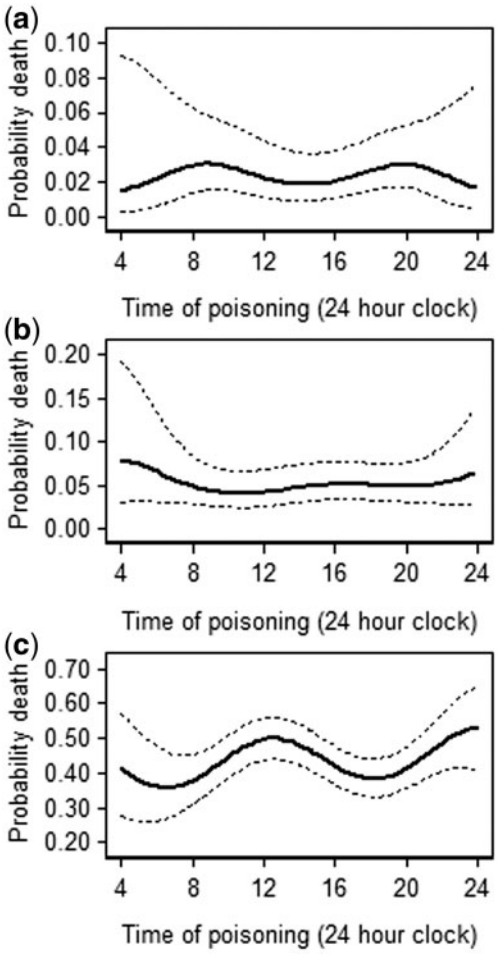

Figure 4 Diurnal variation (95% CIs) in the probability of death following ingestion of (a) glyphosate, (b) all carbamates and (c) paraquat

Discussion

This study provides for the first time strong evidence that human mortality after poisoning is determined in part by the time of poison ingestion. Patients who ingested oleander seeds in the late morning were over twice as likely to die than people who ingested seeds between 16:00 and 24:00. We found no indication that this increased risk was due to patients ingesting more poison during the morning hours. Similarly, delay to hospital presentation and the time of hospital admission, with its related healthcare staffing issues, were also not responsible. Possible delays in temporary pacemaker placement for those ingesting oleander in the early evening and presenting overnight did not correspond to the highest case fatality found for those ingesting the poison in the late morning. Furthermore, there is no evidence that this intervention benefits poisoned patients.[21]

Instead, we hypothesize that increased P-glycoprotein activity at the end of the day reduced absorption in the intestine of oleander seed glycosides, reducing blood concentration and cardiotoxicity. The circadian rhythm of human P-glycoprotein in the intestine is unknown. However, studies of murine intestine have shown a 15-fold increased expression of P-glycoprotein protein and a 3-fold increase in P-glycoprotein function at the end of the light period.[8]

We found some evidence of a circadian risk of mortality with OP insecticides, but here the increased mortality was in the evening: patients who ingested OP insecticides between 12:00 and 24:00 were 1.3–1.4 times more likely to die than people who had ingested between 08:00 and 12:00. However, this finding was not clearly apparent when we looked individually at two OP insecticides that made up 62% of all the OP insecticides in the cohort. The majority of OP insecticides in Sri Lanka are 'thions' (including chlorpyrifos, dimethoate and fenthion) that require activation to their toxic 'oxon' metabolites, usually via Cytochrome P450 3A4 (CYP3A4) at blood concentrations typical of poisoning.[22,23] To complicate matters, these same enzymes are also important for breaking down OP insecticides.[20] This dual role of CYP450s

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might account for the difficulty of resolving circadian rhythms for OP insecticide toxicity. Alternatively, the rhythm may be every 12 h, making estimation more difficult, as suggested by Figures 3B and 4C and recognized for certain body clocks.[2,24]

We found no convincing evidence of diurnal variation in probability of death for people poisoned by carbamates, glyphosate or paraquat. All are active and do not need to be metabolized by CYP450s; only paraquat is known to be a substrate for P-glycoprotein.[25] The clinical relevance of P-glycoprotein activity in paraquat poisoning is unclear.[26]

This result from poisoned patients supports the hypothesis that timing of therapeutic drug administration may be important for clinical effect.[2] Although there are differences between poisoning and therapeutics, the large doses used and the highly variable time of ingestion in the former allowed the chronotoxicity to be clearly detected. The principle can be translated to therapeutic use where timing of drug administration may be important for improving the absorption of drugs. A greater emphasis on altering times of drug administration in drug development and clinical practice to improve pharmacokinetic and dynamic profiles may result in improved effectiveness with reduced toxicity for many drugs.

The cohort on which this study is based has unique strengths. It is large, containing >14 000 patients and 5000 poisoned by a single poison (cardiac glycoside-containing yellow oleander seeds) and with many deaths; data collection was prospective with >99.9% collection of outcome data.[27] Being within the tropics, the seasonal day length did not vary across the year.

We currently lack knowledge of CYP450 and transporter circadian rhythms in human tissue and therefore need to extrapolate circadian rhythms from rodent studies to humans. The only foreseeable data for human expression will be from readily accessible tissues such as peripheral blood leucocytes; however, it is not clear that these tissues accurately represent the situation in the more relevant liver and intestine. It is also doubtful that *in vivo* CYP450 and transporter activity profiling using marker drugs[28] will be relevant to poisoning because the doses are different. *In vitro* studies have shown different CYP450s to be important activators at different OP insecticide concentrations: CYP1A2 is mainly involved at low pesticide concentrations, and CYP3A4 is involved at higher concentrations, whereas CYP2B6 is involved to a lesser degree at all pesticide concentrations.[22]

In conclusion, we have shown for the first time that timing of poison ingestion can affect survival. This evidence for the importance of chronotoxicity suggests that chronotherapeutics is something that should be considered more strongly in drug development and clinical practice. To look for more evidence, it may be possible to repeat the study with acetaminophen poisoning; large datasets are available in the UK, North America and Australia that could be combined and used to validate the findings of studies in mice.[13]

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Conflict of interest: None declared.

KEY MESSAGES

- Medicines and poisons are metabolized by enzymes and transporters with circadian rhythms. The importance of these rhythms to clinical outcome in therapeutic use or after poisoning is unclear.
- In a large Sri Lankan cohort of self-poisoned patients, patients who had ingested oleander seeds in the late morning were three times more likely to die than those who had ingested seeds in the late afternoon and evening.
- A weaker but contrasting effect was seen in patients ingesting OP insecticides, with a greater risk of death in those self-poisoning in the afternoon and evening. No evidence was found of diurnal variation in case fatality in the other pesticides investigated.
- This evidence of chronotoxicity suggests that optimization of administration times during therapeutic drug development may improve the balance of benefit and side effects for some pharmaceuticals.

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