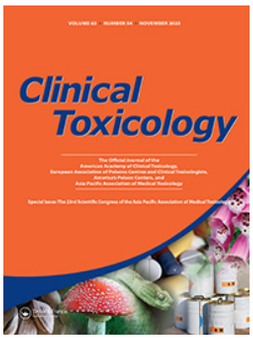

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Outcomes of extra-dose exposures of Vaughan Williams Class I or III antidysrhythmic medications

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ABSTRACT

Introduction: Antidysrhythmic medications are commonly prescribed, but there is little information on the incidence of adverse effects following an inadvertent extra dose of these medications. This poses a challenge to poison centers when trying to decide which patients need to be sent to a healthcare facility for monitoring.

Methods: A retrospective data review of cases reported to a regional poison center between January 1, 2012 and December 31, 2022 was performed. Cases were included if the exposure was a double dose or less of the patient's own antidysrhythmic medication, the exposure was unintentional or a result of therapeutic error, and the antidysrhythmic(s) belonged to Vaughan Williams Class I or III. Cases were included even if other medications were included in the therapeutic error. Descriptive data were collected on cases meeting the inclusion criteria.

Results: One hundred and sixty-two exposures were included. Of these, only 49 were monitored in a healthcare facility for which coded outcomes were available. Of these, the majority had no or minor effects (83.7%). Two of the exposures developed hypotension, but both also involved either a beta-adrenoceptor blocking drug or a calcium-channel blocker. Of the 25 cases that only included an antidysrhythmic, adverse effects were even less common, with 92.0% having no or only minor effects.

Discussion: In this small cohort, adverse events were uncommon with inadvertent extra dose antidysrhythmic exposures. However, serious outcomes have been reported in other studies. It appears adverse events are less common if the extra dose exposure does not involve other cardioactive medications.

Conclusions: Extra-dose exposures of some antidysrhythmics belonging to Vaughan Williams Class I or III were generally well tolerated, but more data are needed to determine whether certain patients can be safely monitored at home. For example, only three cases involved Class IA drugs. Based on our findings, patients who reportedly ingest an extra dose of an antidysrhythmic plus another cardioactive medication should be evaluated at a healthcare facility.

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Antidysrhythmic; double dose; extra dose; poison center; therapeutic error

Introduction

Antidysrhythmic medications are a heterogenous group of xenobiotics used to treat various dysrhythmias [1]. Historically, Vaughan Williams [2,3] classified antidysrhythmic medication into four groups based on their mechanism of action. The drugs colloquially referred to as "antidysrhythmics" generally refer to those in Class I or Class III under the Vaughan Williams classification. Class I constitute medications that block the fast sodium channels, and are further sub-classified into three subclasses: IA, IB, and IC [4]. Examples include procainamide (Class IA), lidocaine (Class IB), and flecainide (Class IC). Class III constitutes medications that block potassium channels. Examples include amiodarone and dofetilide. Drugs belonging to both classes are widely used for the treatment of supraventricular and ventricular dysrhythmias [5,6].

These drugs have a narrow therapeutic index, with several requiring initial dosing to occur in the hospital (e.g., dofetilide). This narrow therapeutic index, combined with the underlying cardiac disease in patients on these medications, poses a concern when inadvertent double doses of these medications occur.

In 2023, cardiovascular drugs were the fifth most frequent substance category enquiry to America's Poison Centers® overall, and a total of 2,489 exposures

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involving an antidysrhythmic were managed [7]. Therapeutic errors are a common cause of exposures reported to poison centers. The most common error involves a patient inadvertently taking their medication twice, with 107,024 calls to America's Poison Centers® for this reason in 2023 [7]. The incidence of adverse effects after a double dose of an antidysrhythmic is unknown. This information is crucial for appropriate risk stratification by poison centers as they provide recommendations for patient disposition.

The objective of this study was to evaluate the incidence of clinical effects reported after an inadvertent extra dose of Vaughan Williams Class I or III antidysrhythmics managed by a large regional poison center.

Method

A retrospective data review of cases reported to a regional poison center between January 1, 2012 and December 31, 2022 was performed. The study was granted an exemption from our institutional review board. We included all pediatric and adult patients who met the following criteria:

1. The exposure was a double dose or less of the patient's own antidysrhythmic medication;
2. The exposure was unintentional or a result of therapeutic error; and
3. The antidysrhythmic(s) belonged to Vaughan Williams Class I or III.

Cases were included even if other medications were included in the therapeutic error.

Cases were excluded if:

1. The exposure was intentional, or if the reason for exposure was unknown;
2. The medication was not the patient's own;
3. The exposure was more than a double dose;
4. The call originated from outside our poison center's catchment area; or
5. Descriptive data were not available.

Further, cases involving only lidocaine or phenytoin were excluded. The former is not used as an antidysrhythmic in pill form, and the latter is mainly used as an antiepileptic. Cases involving only ranolazine were also excluded. Although it has some antidysrhythmic properties, it is generally considered an antianginal medication.

Data extraction was performed by three investigators who were trained for uniform data extraction from our poison center database (ToxiCALL®, Computer Automation Systems, Aurora, CO) using REDCap (Research Electronic Data Capture; Vanderbilt University). The following data were collected if available: patient characteristics (age, sex, concomitant medication exposure), caller site (healthcare facility, home, or other location), poison center disposition (observed home versus sent to hospital for evaluation), interventions (vasopressors, atropine, fluids, or mechanical ventilation), clinical effects, medical outcome (per National Poison Data System® [NPDS®] definition), and duration of effects.

Clinical effects recorded included any documentation of bradycardia, hypotension, occurrence of dysrhythmia, presence of electrocardiogram changes, and occurrence of cardiac arrest. Bradycardia was defined as a heart rate less than 60 beats/min in an adult or below Pediatric Advanced Life Support age-adjusted cutoffs [8]. Hypotension was defined as a systolic blood pressure less than 90 mmHg in an adult or below Pediatric Advanced Life Support age-adjusted cutoffs. Interval changes on the electrocardiogram were defined as a PR interval greater than 200 msecs, QRS complex greater than 110 msec, or QTc greater than 450 msec in males or 470 msec in females. QT correction was performed by the calling hospital by a method of their choosing, but the method was not recorded in the case narratives. These were selected based on the coding criteria utilized by the NPDS®. Electrocardiographic changes were recorded regardless of how it was characterized in the narrative or coding (related, unrelated, or unknown relation to exposure), as, given the retrospective nature, it was impossible to determine this for all cases (without having access to past and present electrocardiograms for each patient). For the medical outcome, the coded outcome at the time of case closure was used. No re-coding was performed, as it was considered that the coding in real time by the poison specialist who took the calls was likely most accurate.

To ensure accurate data extraction, 10% of the total cases were randomly selected from the cases for which data were extracted and reviewed for accuracy by two independent reviewers. Any discrepancies were addressed, and the final decision was made by the lead author.

Results

A total of 379 cases were identified and reviewed. Ultimately, 162 cases met the inclusion criteria (Figure 1). Upon analysis of 10% of all cases to ensure data extraction accuracy, no discrepancies were noted.

Table 1 provides demographic data and descriptive statistics of the exposures included. Most cases involved elderly patients, aged 70 years or older. However, there were three pediatric cases aged ≤5 years. There were slightly more females than males (56.8% female). Most cases involved a double dose of

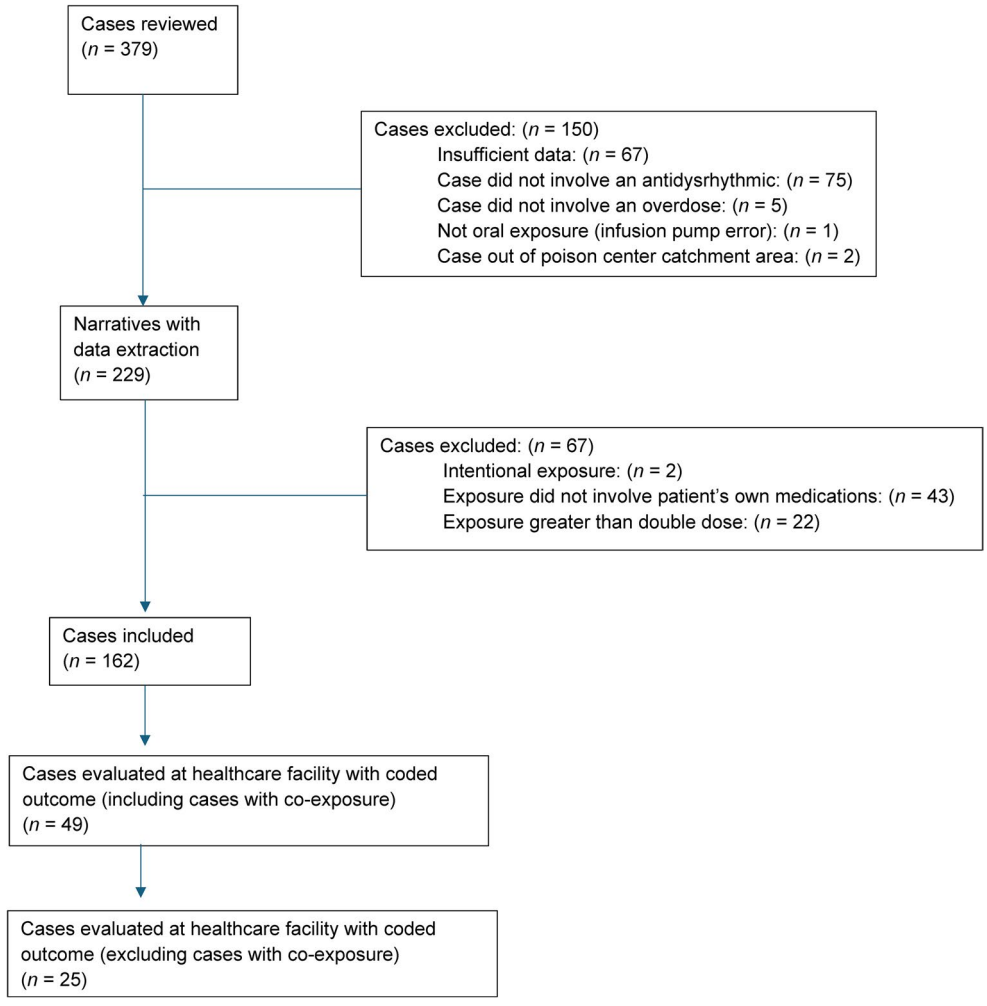

Figure 1. Breakdown of included cases.

Table 1. Demographics and exposure characteristics of included cases ($n = 162$).

Age	*n* (%)
Pediatric	3 (1.9)[a]
Adult (age 20–60 years)	43 (26.5)
Elderly (aged 70 years or older)	77 (47.5)
Unknown adult (age >20 years)	38 (23.5)
Unknown	1
Sex	
Female	92 (56.8)
Presence of co-exposure	
Antidysrhythmic without co-exposure	105 (64.8)
Antidysrhythmic involved	
Amiodarone	41 (25.3)
Disopyramide	2 (1.2)
Dofetilide	38 (23.5)
Dronedarone	26 (16.0)
Flecainide	26 (16.0)
Mexiletine	5 (3.1)
Propafenone	24 (14.8)
Quinidine	1 (0.6)

a. All pediatric patients were ≤5 years old.
b. Total adds up to >162 because one case involved amiodarone and flecainide.

an antidysrhythmic without co-exposure (64.8%). The co-exposures involved were variable. However, looking at the list of reported co-exposures, they were often the other daily medications frequently prescribed to patients on antidysrhythmics. When the drugs involved in the co-exposure could be placed into a general class, cases most often reported antihypertensive medications (38 cases), followed by anticoagulants (22 cases), diuretics (10 cases), cholesterol medications (six cases), or antiplatelet medications (six cases). Twenty-two cases involved a variety of other medications that did not fit well into a dedicated class.

Most calls (72.8%) were received from locations outside a healthcare facility. The additional 27.2% of cases were already at a healthcare facility at the time of poison center contact. Of the 118 cases received from outside of a healthcare facility, 89 (75.4%) were recommended for home observation, while 29 (24.6%) were referred to a healthcare facility. Only 13 of the 29 (44.8%) are known to have arrived at a healthcare facility. An additional patient for whom home care was initially recommended presented to a healthcare facility anyway. In total, 58 cases were seen at a healthcare facility. However, nine of these cases had outcomes coded as "not followed, judged as nontoxic exposure",

"not followed, minimal clinical effects possible," or "unable to follow, judged as potentially toxic". These cases were excluded from the following analysis, leaving 49 cases.

Clinical information was obtained for the 49 patients assessed at a healthcare facility for whom a medical outcome was coded. Table 2 summarizes the clinical outcomes and management of all cases. Compared to the cohort without co-exposure, the cohort that includes all cases (including cases with co-exposure) demonstrated more frequent documentation of bradycardia (34.7% versus 28.0%) and hypotension (4.1% versus 0%). Of note, hypotension was documented in only two cases. Both involved amiodarone and co-exposure with other cardioactive medications, and both exposures developed bradycardia. Fluids were given in both cases, and vasopressors were required in one. Overall, there were more cases coded as having a moderate effect among the total cohort when compared to the cohort without co-ingestion (14.3% versus 8.0%). No case was coded as experiencing a major effect, no patient required mechanical ventilation, and no patient suffered cardiac arrest. Interestingly, 10.2% of all cases documented QRS complex prolongation, and 24.5% of all cases documented QTc prolongation. However, it was not possible to compare the documented values in the poison center documentation to the patient's baseline electrocardiogram, making interpretation of these data limited.

Table 2. Clinical outcomes and management among antidysrhythmic medication extra-dose exposures seen at a healthcare facility with coded outcome.

Clinical effects	Including cases with co-exposure ($n=49$) n (%)	Excluding cases with co-exposure ($n=25$) n (%)
Bradycardia	17 (34.7)	7 (28.0)
Hypotension	2 (4.1)	0
Dysrhythmia	0	0
Electrocardiogram interval change	14 (28.6)	8 (32.0)
Prolonged PR interval	2 (4.1)	1 (3.1)
Prolonged QRS complex	5 (10.2)	2 (8.0)
Prolonged QTc interval	12 (24.5)	6 (24.0)
Cardiac arrest	0	0
Treatment		
Vasopressors	1 (2.0)	0
Atropine	0	0
Intravenous fluids	2 (4.1)	0
Mechanical ventilation	0	0
Activated charcoal	1 (2.0)	0
Coded outcome		
No effect	32 (65.3)	19 (76.0)
Minor effect	9 (18.4)	4 (16.0)
Moderate effect	7 (14.3)	2 (8.0)
Major effect	0	0
Unrelated effect	1 (2.0)	
Coded management site		
Treated/evaluated and released	42 (85.7)	23 (92.0)
Admitted to critical care unit	2 (4.1)	0
Admitted to non-critical care unit	5 (10.2)	2 (8.0)

Table 3 describes the incidence of clinical outcomes for each individual antidysrhythmic. In the total cohort, the antidysrhythmic with the most cases with documented bradycardia was amiodarone (62.5% of cases), followed by dofetilide (40.0% of cases). The only antidysrhythmic with cases documented to have hypotension was amiodarone (two cases), but both those cases involved co-ingestion with other cardioactive drugs.

Most cases were coded as no effect or minor effect, but 33.3% of amiodarone cases, 15.0% of dofetilide cases and 16.7% of dronedarone cases were coded as moderate effect (Table 3). Looking at cases coded as moderate, the three amiodarone cases all involved co-exposure with other cardioactive drugs (verapamil in one case, metoprolol in one case, and metoprolol and isosorbide in another case). The dronedarone exposure coded as moderate also involved co-exposure with another cardioactive drug (carvedilol). However, among the three cases of dofetilide coded as moderate, two did not involve co-exposure, and the one that did include co-exposure involved dabigatran.

Table 3. Rates of select adverse effects and coded outcome for individual antidysrhythmic medications evaluated at a health care facility with coded outcome (including cases with co-exposure) ($n=49$).

Total cohort ($n=49$)	Amiodarone ($n=9$) n (%)	Disopyramide ($n=1$) n (%)	Dofetilide ($n=20$) n (%)	Dronedarone ($n=6$) n (%)	Flecainide ($n=7$) n (%)	Mexiletine ($n=1$) n (%)	Propafenone ($n=5$) n (%)
Adverse effects							
Bradycardia	5 (62.5)	0	8 (40.0)	2 (28.6)	1 (14.3)	0	1 (20.0)
Hypotension	2 (25.0)	0	0	0	0	0	0
QRS complex prolongation	1 (12.5)	0	1 (5.0)	0	3 (42.9)	0	0
QTc prolongation	1 (12.5)	0	7 (35.0)	2 (28.6)	2 (28.6)	0	0
Case severity							
No effect or minor effect	6 (66.7)	1 (100.0)	17 (85.0)	5 (83.3)	6 (85.7)	1 (100.0)	5 (100.0)
Moderate effect	3 (33.3)	0	3 (15.0)	1 (16.7)	0	0	0
Major effect	0	0	0	0	0	0	0
Unrelated effect	0	0	0	0	1 (14.3)	0	0

Discussion

In this retrospective cohort study, 49 patients who experienced an extra dose exposure to their Vaughan Williams Class I or III antidysrhythmic were evaluated at a healthcare facility. Overall, patients did well, with no case coded as experiencing a major outcome. Most cases were observed and discharged home without requiring admission. None of the patients with an isolated antidysrhythmic extra dose developed hypotension (95% CI: 0–12%, calculated by the Rule of Three), but two patients who were co-exposed to other cardioactive medications did develop hypotension. Most of the cases coded as experiencing a moderate outcome involved co-exposure to other cardioactive medications, suggesting this is a risk factor that should prompt evaluation at a healthcare facility.

Previous studies investigating therapeutic errors involving antidysrhythmics suggest that most cases develop no or very minor adverse effects [9]. However, some report development of major effects necessitating advanced treatments and monitoring in the critical care setting [10–12]. A retrospective analysis of double-dose exposures in one poison control system identified one case of a double dose of propafenone resulting in a major effect [10]. A 59-year-old female who was exposed to propafenone 150 mg (double dose) developed syncope, ventricular tachycardia, and first-degree atrioventricular block [10]. She was cardioverted, started on lidocaine drip and was admitted to the intensive care unit.

The package insert for dofetilide describes a case of a double dose of 500 µg, separated by one hour, developing ventricular fibrillation and cardiac arrest [11]. Further information in this case is lacking. A conference abstract [12] found that half of the cases with unintentional dofetilide therapeutic errors remained asymptomatic, while 47% were admitted due to cardiovascular toxicity.

Although it is reassuring that cases involving an extra dose of an antidysrhythmic without co-exposure in our cohort did well overall, this cohort was very small. As described above, serious outcomes have been documented in other publications. Our data are insufficient, and more research needs to be done to determine if patients exposed to an extra dose of an antidysrhythmic alone without co-exposure can be safely monitored at home, depending on the drug, dose, or underlying patient characteristics. However, our data do suggest that patients exposed to an extra dose of an antidysrhthymic with other cardioactive medications should be evaluated at a healthcare facility.

It is interesting to note that, of the 30 patients for whom the poison center recommended healthcare facility evaluation, only 44.8% are known to have presented to a healthcare facility. This is similar to previously reported poison center data, where only 44.6% of callers referred for health care evaluation for a bupropion double dose presented to a healthcare facility [13]. Providing more information to callers may encourage them to heed the advice of the poison center.

Limitations

There are limitations to this study. Most significantly, the sample size of this cohort is small, and the individual antiarrhythmics are variable in their toxicity. Combining all of them into one small cohort limits the applicability to each medication individually. Further, the study only focused on cases that presented to a healthcare facility, so there may have been a bias toward more symptomatic exposures.

The study is retrospective in nature, so the typical limitations of retrospective chart reviews apply - most notably the lack of confirmation of exposure and the inability to determine if the interval changes on electrocardiogram or heart rate were different from the patient's baseline.

Similarly, as described in the methods, abnormal vital signs or electrocardiogram intervals were only documented if present, and some cases may not have mentioned a full set of vital signs or explicitly provided the electrocardiogram intervals. Therefore, the true incidence of abnormal vital signs or electrocardiogram intervals may be higher than described. Also of note, the electrocardiogram interval cutoffs used for this study are perhaps less consistent with clinical significance (notably the QTc cutoffs); however, these data were consistent with NPDS® coding criteria.

Unfortunately, it was not possible to determine how long patients were observed in the healthcare facility, and there was likely variation between cases. It is possible that an adverse event occurred after clearance from the healthcare facility or after the poison center stopped following the case.

Finally, the reviewers were not blinded to the study question and hypothesis. Therefore, bias may have been present in the narrative reviews, though mitigation was attempted through independent re-review of 10% of cases.

Conclusions

Extra-dose exposures to antidysrhythmics are generally well tolerated, but more data are needed to determine whether certain patients can be safely monitored at home. However, the data presented here do suggest

that patients who ingest an extra dose of an antidysrhythmic plus another cardioactive medication should be evaluated at a healthcare facility.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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