

Drug related adverse events due to cardiotropic agents : Epidemiology and prognosis in the emergency department

Profil épidémiologique et pronostique des patients consultant aux urgences pour surdosage en cardiotropes

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RÉSUMÉ

Introduction : La gravité du surdosage en cardiotropes est liée au risque de retentissement cardiovasculaire mettant en jeu le pronostic vital. Leur toxicité est imputée à leur marge thérapeutique étroite. La présentation clinique reste toutefois polymorphe et représente un challenge pour le médecin urgentiste afin de rattacher l'imputabilité à ce type d'iatrogénie.

Objectif : Etudier le profil épidémiologique et pronostique des patients consultant aux urgences dans un tableau compatible avec un diagnostic d'iatrogénie aux cardiotropes.

Méthodes : Etude prospective monocentrique sur 12 mois. Inclusion de patients âgés de plus de 18 ans chez qui l'iatrogénie aux cardiotropes a été retenue. L'effet indésirable médicamenteux (EIM) lié aux cardiotropes a été sélectionné après décision collégiale. Le pronostic a été évalué en termes de gravité et de mortalité à J30. Une analyse univariée a été réalisée. Un $p < 0,05$ était significatif.

Résultats : Nous avons inclus 51 patients. L'âge médian était de 72 ans, le sex-ratio de 0,64 avec prédominance féminine. Vingt cas de mésusage ont été recensés (39%) avec dans 51% des cas liés au prescripteur. L'EIM a été jugé grave dans 45% des cas et le taux de mortalité à J30 a été chiffré à 12%. Les classes médicamenteuses ont été dominées par les bêta-bloquants chez 20 patients (39%) et l'amiodarone chez 18 patients (35%). Les bêta-bloquants étaient significativement les plus incriminés dans la survenue d'un EIM grave. Une double iatrogénie a été retrouvée chez 13 patients (25%). Le mésusage et l'EIM lié au prescripteur ont été retrouvés comme facteurs prédictifs de la gravité de l'EIM en analyse univariée avec respectivement : (OR brut=22; IC95%=[5,2 ;93,5] ; $p < 0,001$) et (OR brut=3,7 ; IC95%=[1,1 ;12] ; $p = 0,015$). L'insuffisance rénale (OR brut=5,8 ; IC95%=[1,3 ; 26,5] ; $p = 0,015$) ; le mésusage (OR brut=16,7 ; IC95%=[1,9 ;143,5] ; $p = 0,002$) et l'EIM grave (OR brut=15 ; IC95%=[1,75 ; 129] ; $p = 0,005$) ont été retrouvés comme facteurs prédictifs de la mortalité à J30 en analyse univariée.

Conclusion : Cette étude a montré que l'iatrogénie due aux cardiotropes est fréquente et représente une situation grave essentiellement chez les sujets âgés. Les Bêta-Bloquants étaient la classe médicamenteuse la plus souvent représentée dans la moitié des cas, l'EIM est évitable et lié au prescripteur.

Mots-clés

Pronostic, mortalité, cardiotropes, iatrogénie, urgences

SUMMARY

Summary: The severity of cardiotropic agents overuse is related to the risk of cardiac and hemodynamic life-threatening situations. Toxicity is attributed to their narrow therapeutic spectrum and pharmacodynamic properties. The clinical presentation, however, remains polymorphic and represents a challenge for the emergency physician to relate accountability to the exact agent. The aim of this study was to evaluate epidemiological, clinical and prognostic profile of patients visiting emergency department in whom iatrogeny secondary to cardiotropic use was diagnosed.

Methods: This was a single-center prospective study over 12 months. We included successively all patients aged over 18 years in whom diagnosis of cardiotropic iatrogeny was made. Cardiotropic related drug-induced events were selected after collegial decision making processing. Prognosis was evaluated in terms of severity and mortality at day 30. Univariate analysis was conducted. $P < 0.05$ was significant.

Results: We enrolled 51 patients. Median age was 72 years with IQR (25,75) of (62,78). Sex ratio was 0.64. Twenty cases of misuse were identified (39%) with 51% of cases being related to the physician. Accountability of the adverse drug event (ADE) was 51%. The ADE was considered severe in 45% of cases and the death rate on day 30 was 12%. Drug classes were dominated by beta-blockers in 20 patients (39%) and anti-arrhythmic agents (Amiodarone ®) in 18 patients (35%). Beta-blockers were significantly the most incriminated in the occurrence of severe ADE. A double iatrogeny was found in 13 patients (25%). Misuse and physician-related ADE were found to be predictive of the severity of ADE in univariate analysis with respectively: For misuse: (OR brut=22, CI95%=[5.2;93.5] ; $p < 0.001$) and for related physician ADE (OR brut = 3,7 ; CI95%=[1.1;12] ; $P = 0.015$). Predictive factors of mortality at day 30 in the univariate analysis were: Past renal failure : OR brut 5,8; CI95%[1,3-26,5]; $p = 0,015$; misuse with OR brut=16,7, 95% CI=[1.9-143.5], $p = 0.002$ and severe ADE with OR brut=15, 95% CI=[1.75-129], $p = 0.032$.

Conclusion: This study showed that ADE related to Cardiotropic agents are frequent and remain a serious condition especially in elderly. Betablockers agents were the mostly incriminated therapeutic class in the severity of the clinical condition by its hemodynamic repercussions responsible of a high rate of hospitalizations and mortality. Misuse and physician-related ADE were found to be predictive of the severity. Whereas, occurrence of severe ADE, misuse and past renal failure were predictive of mortality. Moreover, in 51% patients, ADE was preventable and related to the prescription of physician showing the main role of the preventability and the role of the prescriber in the genesis of this severe condition.

Key-words

Prognosis, Mortality, Cardiotropic agents, Drug related events, Emergency department

BACKGROUND

Drug related adverse events or iatrogeny is a common situation in emergency medicine but remains often under-diagnosed because of the overall polymorphic clinical presentation. This situation has been defined by the World Health Organization (WHO) as any adverse and unwanted event that may be related to the usual doses of a drug used for the prophylaxis, diagnosis, treatment of a disease, or to modify physiological functions [1]. The WHO also defined iatrogeny in 1969 as any harmful and unwanted reaction related to medication and occurring accidentally [2]. The High Council for Public Health (HCSP) defines iatrogeny as an undesirable or negative consequence on the individual or collective state of health of any act or measure practiced or prescribed by an authorized professional aimed at preserving, improving or restoring health [3,4]. Anglo-saxons substitute the term iatrogenic by an "Adverse-event" [5]. Some attribute iatrogeny to a positive response to discontinuation of treatment within 48 hours [6]. According to Edwards and Aronson, the ADE is defined as a harmful or unpleasant reaction related to the use of a drug, which could lead to danger in case of subsequent administration and justify prevention, specific treatment, changing doses or discontinuation of the product [7]. Cardiotropic agents are widespread and largely used especially with aging population and cardiovascular leading diseases. Moreover, poly medication is frequent in elderly exposing to the settlement of this pathology. It has been demonstrated that iatrogeny is correlated to poor prognosis and represents a public health problem burdened with a heavy morbi-mortality [8]. Cardiotropic iatrogeny is the second leading cause of toxic death in the United States [9]. Cardiotropic iatrogeny is life-threatening situation frequently encountered in the emergency field but remains under-estimated inducing a lack of sufficient epidemiological data. Pharmacological specificity of cardiotropic agents is characterized by the strong binding to plasma proteins and a large volume of distribution. Clinical presentation, however, remains polymorphic and represents a challenge for emergency physicians to relate accountability to this drug.

The aim of this study was to evaluate the epidemiological, clinical and prognostic profile of patients presenting to the emergency department with final diagnosis of cardiotropic related iatrogeny retained.

METHODS

Study design:

This was a prospective observational and single-center study conducted in an ED of a teaching hospital with 125.000 annual visits. Patients were enrolled prospectively over 12 months (March 2012 to March 2013). Data were prospectively collected on a pre-established check-list with demographic, clinical, biological and evolution findings. We included all patients aged over 18 years in whom diagnosis of cardiotropic iatrogeny was retained after evaluation and collegial decision making of the imputability of the responsible drug and the probability of iatrogeny. We didn't include voluntary poisoning, iatrogeny acquired after admission for another initial health problem and non-pharmacological adverse event (linked to invasive technical procedures). Patients in whom data were incomplete were excluded.

Main outcome was evaluated by the occurrence of severe ADE at admission or emergency management and mortality at day 30. Patients were assessed for severity and considered at high-risk with serious ADEs if they fulfilled any of the following criteria: Hemodynamic instability (defined by a systolic blood pressure (SBP) < 90 mmHg), bradycardia (less than 40 bpm), severe conduction or rhythm disturbances and impairment of neurological status (GCS<13). Severity was assessed by Ambulatory Simplified Severity Index (IGSA). Moreover, for each patient with an ADE, the event was assessed for occurring of two factors: Misuse and preventability. Misuse was furthermore analyzed for being part of a physician prescription or due to patient itself.

For follow-up, patients or their relatives or hospitalization ward were contacted by phone at day 30 to check evolution.

We conducted a comparative study to assess the severity and mortality at day 30, followed by univariate analysis.

Definitions

Misuse: a use that is not in accordance with the summary of product characteristics.

Evitability: identification of adverse effects that can be prevented and seeks to propose preventive actions to reduce risks.

Adverse drug event (ADE): harmful and unwanted reaction occurring at doses normally used in humans for the prophylaxis, diagnosis or treatment of a disease, or for the restoration, correction or modification of a disease or a

physiological function, or resulting from misuse of the drug or product. The adverse drug event (ADE) may be related to the prescriber or the patient himself.

An ADE was considered severe in the presence of one or more of the following criteria:

- Respiratory, circulatory and / or neurological distress.
- Need for an initial evaluation in the emergency resuscitation room (ERR).
- Need to hospitalization and / or intensive care unit supervision: cardiology intensive care unit (CICU), close emergency unit (USR) or resuscitation unit.
- Use of intensive therapeutic means: vasoactive and / or inotropic drugs; external electric shock (EES); mechanical ventilation (MV) and need for a technical gesture in emergency: systolic training catheter, pacemaker..
- Death.

Statistical analysis:

Statistical Package for Social Sciences (SPSS 20.0, IBM) for analysis was used. Gaussian distribution nature of each quantitative variable was verified using the Kolmogorov-Smirnov test to guide the subsequent statistical study. In all statistical tests, the significance level $p < 0.05$ was considered significant. Variables with normal distribution were expressed as mean \pm standard deviation, while quantitative variables with non Gaussian distribution were expressed in median and 25th and 75th IQR. Univariate analysis was conducted.

RESULTS

Characteristics of the population:

During the study period, 165 cases of pharmacological iatrogeny managed in the ED were collected over the 12 months period. Iatrogeny related to cardiotropic agents was collected in 51 patients. The incidence was 0.45 %. Median age was 72 years: IQR (25^e,75^e)=(62, 78). Twenty per cent of the patients were aged more than 80 years. Sex-ratio was 0.64 with female predominance. Forty-nine patients (96%) arrived in the ED by their own means. The table 1 illustrates medical past history of patients.

Vital signs at presentation were: Systolic Blood Pressure (SBP)<90 mmHg in 10 patients (20%); Cardiac Frequency (CF)< 50 bpm in 30 patients (59%); Pulse Oximetry (SpO2)< 90% in 6 patients (12%) and Glasgow Coma Scale (GCS)≤13 in 5 cases (10%). Vertigo and dizziness were the leading reasons for consultation in 33% and

27% of cases respectively, followed by dyspnea in 14% of cases. Twenty-six patients (51%) had serum creatinine greater than 120 micromoles/l, of which 10 (20%) were known to have renal failure. Eight patients (16%) had hyperkalemia on admission and 3 patients (6%) had hypokalemia. Mean IGSA was 5.5 ± 2.6 with extremes of 0 and 12. Thirteen patients (25%) had an IGSA ≥8.

Analysis of the medical prescription:

The average number of drugs consumed daily by patients was 5 ± 1 with extremes of 1 to 10 drugs. Thirty patients (59%) consumed at least 5 drugs. Moreover, fifteen patients (30%) ignored the name of the drug and 9 patients (18%) did not know the related effects. A double cardiotropic iatrogeny was found in 13 patients (25%). The incriminated drug classes were dominated by beta-blockade agents in 20 patients and anti-arrhythmic agents (Amiodarone ®) in 18 patients as shown in table 2.

Treatment required at the emergency department:

Seventeen patients (33%) required optimization of circulatory state with isotonic saline, and 9 of them (18%) required vasopressors agents. No patient required mechanical ventilation. Thirty-nine patients (76%) were hospitalized in ED. Twelve patients (23%) were discharged home the same day.

Analysis of the adverse drug event: Severity and Mortality

Misuse was found in 26 patients (51%). ADE was related to the prescriber in 27 cases (53%) and related to the patient in 9 cases (18%). ADE was preventable in 26 patients (51%). It was severe in 27 cases (53%).

Physician-related ADE and misuse were identified as predictive factors of severe ADE in univariate analysis.

Mortality rate at day 30 was 23% (12 cases).

Table 3 summarizes the comparison of the severe and non-severe ADE groups in univariate analysis.

Renal failure, misuse and severe ADE were found to predict mortality at day 30 in univariate analysis.

Table 4 summarizes the comparison of groups of deceased versus survivors in univariate analysis.

DISCUSSION

In the present study, it has been shown that misuse due to patient and physician-related ADEs were found to be

predictors of severity and that past renal failure, misuse and severe ADEs were found to be predictors of mortality at day 30 in patients visiting the emergency department with iatrogeny related to cardiotropic agents. Incidence in our emergency population was estimated to a number of 0.45 %. There are not many studies evaluating the occurrence of cardiotropic iatrogeny and numbers in emergency medicine remain low.

Baseline characteristics of the ADE:

This study showed that the onset of severe ADE (53%) was primarily related to misuse, physician prescription and double iatrogeny conditions, which are therefore preventable factors. Their knowledge would prevent their occurrence and guide the therapeutic approaches in patients requiring treatment with cardiotropic agents. The rate of preventability was 51%, approaching the numbers found in the literature [10,11].

ADE was preventable in 15 patients who had severe ADE (55%) and in 3 patients who died (25%). In the literature, the incidence of severe ADEs has not changed in five years [12].

Iatrogeny and difficult clinical decision making:

The medical management of acute intoxications is the most often motivated by the presence of neurological signs [13]. In this study, more than half of the patients (n=31; 60%) presented to the ED for vertigo, dizziness or lipothymia. Those are non-pathognomonic signs and do not lead to a clear diagnosis pathway. Clinical decision making in such situations is already difficult and may expose to both delay in identifying the causable agent and in triggering treatment in adequate time. Emergency physician may be aware of the possibility of iatrogeny as responsible of some neurological signs.

Drug class incriminated:

In this study, beta-blockers and amiodarone were mostly the responsible agents with 39% and 35% of cases respectively followed by calcium channel blockers (22%) and digitalics (14%). Beta-blockers were most related to mortality (67%; $p = 0.031$).

Beta-blockers and calcium channel blockers represent the cardiotropic agents most widely used in the world. In overdose, they have similar effects, mainly hypotension and bradycardia by a myocardial depression effect. In addition, calcium channel blockers can induce vasoplegia

that triggers the onset of hypotension and shock [14,15]. Calcium channel blockers and beta-blockers account for approximately 40% of cardiotropic iatrogeny according to "The American Association of Poison Control" and account for more than 65% of deaths due to cardiotropic drugs [16,17].

Severity assessment:

In our study, severe ADE occurred in 27 patients (53%). Severity was primarily related to misuse, physician prescription and double iatrogeny, which are, therefore, preventable factors. In another retrospective study conducted in Korea over two years (2005-2007), the factors most related to the occurrence of severe bradyarrhythmia were the history of coronary artery disease, ventricular arrhythmia, impaired systolic function, advanced age and double iatrogeny [6]. In another retrospective study [18], the factors related to the occurrence of severe bradycardia were advanced age and double iatrogeny.

Therapeutic issues:

The presence of a state of shock during intoxication is synonymous of increasing mortality.

Compared to other clinical presentations of different iatrogenies, cardiotropic mortality is the mostly related to cardiocirculatory failure.

The usual symptomatic therapeutic means (volume expansion, vasopressors, molar sodium bicarbonates..) are in many cases insufficient.

Tonic heart failure is dynamic, transient and reversible, depending on the pharmacokinetics of the toxic, it is therefore legitimate to resort to peripheral circulatory assistance, allowing to reduce the concentration of the toxic in target organs by maintaining its renal and hepatic elimination [19].

The indication of a temporary pacemaker has been posed in some studies in iatrogenic bradycardia [15,20].

The indication of a permanent pacemaker has been also discussed, especially in particular and serious cardiac conditions. One study showed that in almost 25% of cases, bradycardia was not due to drugs but revealed by drugs, indicating the permanent pacemaker [6].

External electro systolic training does not seem ineffective in the majority of cardiotropic toxicities because of a lack of inotropism [14]. It remains a remedy in the absence of isoprenaline.

Is there a toxic dose for cardiotropics ?

Determining an exact toxic dose is difficult given the inter-individual variability, polymedication and frequent drug interactions [14].

Thus, in a clinical review elaborated by Baud F and al, minimum or threshold doses of the main toxic cardiotropics, or more precisely the presumed ingested doses (PID) expected to cause early serious cardiovascular disorders which may even require circulatory assistance, have been defined to help and guide primary care physicians (emergency physicians, EMS regulatory physicians, etc.) to assess and estimate the severity of cardiotropic iatrogeny at an early stage [21].

However, the time elapsed between ingestion and clinical evaluation is crucial to judge the severity of the iatrogeny and not underestimating it.

Limits:

The limitations of this study were represented by the small size, the single-center character and the non-adoption of a scale to judge the avoidance nature of the ADE.

Perspectives and prevention:

The role of the physician is well before the arrival of the patient in ED: it is therefore essential in the genesis of iatrogeny.

In our study, we identified 26 prescriber-related ADE cases (51%) and the same for the preventability.

The role of continuing education and teaching hospitals has been demonstrated in the study of Thomas and al [22] in the prevention of iatrogeny, finding a lower incidence of ADEs in teaching hospitals compared to first-line structures and regional hospitals.

CONCLUSIONS

This study showed that adverse drug events due to cardiotropic agents are frequent. Clinical presentation of cardiotropic iatrogeny is polymorphic and represents a challenge for the emergency physician to relate accountability to one drug. Beta-blockers and calcium channel blockers were the classes the most widely used. In our work, an ADE was considered severe in 45% of cases and the death rate at day 30 was 12%. The beta-blockers were in the lead of the most incriminated drugs in cardiotropic iatrogeny and in the occurrence of severe ADE. Severity was primarily related to misuse and physician prescription, which are, therefore, preventable

factors. Renal failure, misuse and severe ADE were found to predict mortality at day 30. Preventing the occurrence of these ADE is part of the role of the emergency physician.

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