LISTE DES ABREVIATIONS

ANSES	Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail
BNCI	Banque Nationale des Cas d'Intoxication
CAPTV	Centre Antipoison et de Toxico Vigilance
CNIL	Comission Nationale de l'Informatique et des Libertés
GFR	Glomerular Filtration Rate
GCS	Glasgow Coma Score
LA	Lactic Acidosis
MALA	Metformin Associated Lactic acidosis
PSS	Poison Severity Score
SiCAP	Système d'information des Centres
T2D	Type 2 Diabetes

PLAN

Metformin overdose: a serious iatrogenic complication

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RESUME

Background: The prevalence of type-2 diabetes continues to rise across the world. Metformin is still the gold standard and is thereby increasingly prescribed. Monitoring of metformin continues to be debated because of its association with lactic acidosis, a rare but life-threatening complication. The aim of this study is to describe metformin poisoning in the general population and to highlight the main risk factor for severe poisoning.

Methods: Retrospective study of metformin poisoning from September 1999 to September 2016 at Angers University Hospital's Poison Control Centre. The primary endpoint was mortality. Secondary endpoints were high gravity (grade 3) and cardiovascular shock.

Results: 382 cases of metformin poisoning were included: 261 cases of "null severity" (grade 0), 40 cases of "mild severity" (grade 1), 14 cases of "moderate severity" (grade 2) and 67 cases of "high severity" (grade 3). We listed 21 deaths in this series: 71% therapeutic accident and 29% self-poisoning.

Circumstance of therapeutic accidents and an episode of diarrhoea were associated with a higher risk of mortality. The same risk factors are found for severe gravity and cardiovascular shock.

Conclusions: Type 2 diabetic patients treated with long-term metformin may experience serious iatrogenic complications. Monitoring of their treatment should be taken seriously especially in the event of digestive symptoms such as diarrhea.

INTRODUCTION

Le diabète de type 2, pathologie qualifiée d'épidémie mondiale est devenue une préoccupation majeure de santé publique. Dans cette pathologie, la metformine a un rôle central car il s'agit du traitement recommandé en première intention après l'échec des mesures hygiéno-diététiques en cas de découverte de diabète de type 2. Elle appartient à la classe des biguanides, commercialisée depuis les années 1950.

Les principaux effets indésirables de la metformine sont les symptômes digestifs (nausées, dyspepsie, douleurs abdominales) et plus rarement l'acidose lactique. Malgré des règles de prescription bien établies avec une contre-indication chez les insuffisant rénaux sévères et la nécessité d'une surveillance étroite dans la population gériatrique de plus de 75 ans ("10irp04_reco_diabete_type_2.pdf," n.d.), il est observé de manière non exceptionnelle des cas d'intoxication graves pouvant conduire au décès.

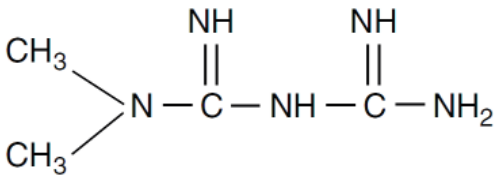
Cette étude rétrospective au Centre Antipoison et de Toxicovigilance (CAPTV) d'Angers de septembre 1999 à septembre 2016 a pour objectif de mieux décrire les cas d'intoxication à la metformine et d'en analyser les principaux facteurs de risque de sévérité.

METFORMINE

1. Structure

La metformine est une molécule de poids moléculaire de 165 Da. Il s'agit du N,N-diméthylbiguanide (Figure 1). La molécule de metformine est une base faible très polaire et très hydrosoluble.

Figure 1 : Molécule de metformine



2. Pharmacologie

La metformine fait partie de la classe des biguanides. Elle a un rôle anti hyperglycémiant grâce à différents effets. Son principal rôle est de diminuer l'hyperglycémie en diminuant la production de glucose hépatique par inhibition de la néoglucogénèse et de la glycogénolyse. Elle permet également de contrôler la glycémie post prandiale en favorisant la captation et l'utilisation de glucose au niveau musculaire et en retardant son absorption au niveau intestinal.

La metformine a également des effets bénéfiques sur le métabolisme lipidique en réduisant le cholestérol total, le LDL-cholestérol ainsi que les taux de triglycérides.

3. Pharmacocinétique

Après administration par voie orale, la metformine est absorbée au niveau de l'intestin grêle avec une biodisponibilité de l'ordre de 50 à 60%. La demi-vie d'absorption est estimée entre 0,9 et 2,6 heures avec un pic de concentration plasmatique atteint en 1 à 2 heures pour une dose de 500 à 1000 mg.

La liaison aux protéines plasmatiques est négligeable. La metformine diffuse dans le secteur plasmatique et intracellulaire, notamment les érythrocytes, qui représentent très probablement un compartiment secondaire de distribution.

La demi-vie apparente d'élimination est d'environ 6,5 heures. La metformine est excrétée sous forme inchangée par voie rénale, par sécrétion tubulaire, avec une clairance rénale supérieure à 400 mL/mn. En cas d'insuffisance rénale, son accumulation est proportionnelle au taux de créatininémie.

4. Indications et contre-indications

Les indications de la metformine, en France, sont le traitement du diabète de type 2, en particulier en cas de surcharge pondérale, lorsque le régime alimentaire et l'exercice physique

ne sont pas suffisants pour rétablir l'équilibre glycémique. Elle peut être utilisée en monothérapie ou en association avec d'autres antidiabétiques oraux ou avec l'insuline.

La dose initiale d'introduction de la metformine est de 500 mg deux fois par jour. La dose peut être majorée par pallier de 500 mg par jour, en deux à trois prises avec une dose maximum de 3000 mg/jour. Une augmentation progressive de la posologie peut permettre d'améliorer la tolérance gastro-intestinale.

La metformine a montré son efficacité sur la réduction de la mortalité et la diminution des complications cardiovasculaires notamment les infarctus du myocarde chez les patients diabétiques de type 2 avec une surcharge pondérale.

Il est recommandé de ne pas dépasser la dose de 1500 mg/jour et de surveiller de manière accrue la fonction rénale chez les patients présentant une insuffisance rénale avec une clairance comprise entre 30 et 60 mL/min compte tenu d'un risque plus important d'acidose lactique.

Les contre-indications de la metformine sont :

- hypersensibilité à la metformine ou à ses excipients ;
- acidocétose diabétique ;
- insuffisance rénale chronique avec une clairance inférieure à 30 mL/min ;
- affection aigue susceptible d'altérer la fonction rénale telle qu'une déshydratation, un choc, une infection grave ou l'administration de produit de contraste iodé ;
- maladie aigüe ou chronique pouvant entrainer une hypoxie tissulaire telle qu'une insuffisance cardiaque ou respiratoire, un infarctus du myocarde récent, ou un choc ;
- insuffisance hépatocellulaire ("Résumé des caractéristiques du produit - GLUCOPHAGE 1000 mg, comprimé pelliculé sécable - Base de données publique des médicaments," n.d.).

5. Principaux effets indésirables

Les effets secondaires les plus courants sont d'ordres gastro-intestinaux avec des douleurs abdominales, et des diarrhées. Ces effets secondaires sont le plus souvent transitoires et cessent à l'arrêt du traitement.

La complication principale de l'intoxication par la metformine est la survenue d'une acidose lactique.

Le mécanisme de survenue d'une acidose lactique chez les patients traités par metformine est complexe et multifactoriel. L'inhibition de la néoglucogenèse hépatique empêche la métabolisation du lactate produit par le muscle et surtout l'inhibition du complexe I de la chaîne respiratoire accélère la glycolyse, oriente le métabolisme vers un fonctionnement anaérobie et aboutit à une baisse de la consommation d'oxygène et à la production de lactates (Fourrier and Seidowsky, 2010).

6. Surdosage

Un surdosage important de metformine ou l'existence de risques concomitants peuvent conduire à une acidose lactique. Il convient de doser les taux sérique, plasmatique ou sanguin de metformine pour confirmer le diagnostic, évaluer le pronostic d'une intoxication et suivre l'efficacité du traitement. Avec une posologie thérapeutique, ce taux est de 1 à 4 mg/l (Netgen, n.d.).

Les principes du traitement de l'acidose lactique reposent sur la correction de l'acidose métabolique, l'épuration de la metformine et le traitement d'une éventuelle pathologie intercurrente. L'épuration extrarénale est la technique de référence en cas d'acidose métabolique par intoxication médicamenteuse surtout si elle est associée à une insuffisance rénale (Fourrier and Seidowsky, 2010).

MÉTHODES

Il s'agit d'une étude rétrospective descriptive de cas anonymisés d'intoxications dans la population générale, toute gravité confondue impliquant la metformine, de septembre 1999 à septembre 2016 au Centre Antipoison et de Toxicovigilance (CAPTV) d'Angers, enregistrés dans la base nationale des cas d'intoxications (BNCI).

Le critère d'inclusion a été défini par l'exposition à la metformine dans la population avec ou sans symptômes. Les critères d'exclusions étaient tous les cas de co-intoxication avec des effets secondaires autres que ceux de la metformine et ceux présentant un diagnostic n'étant pas d'origine toxique.

Les données continues ont été résumées en utilisant la moyenne + -SD ou la fourchette médiane et inter-quartile, et comparées en utilisant les tests de Mann et Whitney. Les données catégorielles ont été résumées en utilisant des nombres et des pourcentages et comparées en utilisant des tests exacts de Fisher.

La méthode de recueil et d'analyse de cette étude est détaillée dans l'article ci-dessous.

RÉSULTATS : METFORMIN OVERDOSE : A SERIOUS IATROGENIC COMPLICATION

1. INTRODUCTION

Between 2000 and 2009, the prevalence of patients treated for diabetes increased from 2.6% to 4.4% and their number from 1.6 to 2.9 million in France. The prevalence of type-2 diabetes (T2D) continued to rise beyond experts' forecasts, especially with a high prevalence in the population over the age of 60 years (Ricci et al., n.d.). Metformin is acknowledged worldwide as playing a pivotal role in the primary treatment of T2D (Kajbaf et al., 2013). It is a biguanide, introduced in 1957 along with Phenformin and Buformin. The last two were withdrawn in the 70's due to a high incidence of lactic acidosis (LA) (Bailey, 2017). Metformin use has increased steadily from 24% of treatment visits in 1997 to 53% in 2012,

according to an American study (Turner et al., 2014), and in a recent French study, ENTRED, 62% of T2D were treated with a biguanide ("rapport-entred.pdf," n.d.). The two studies show that metformin is the most commonly used treatment in T2D today and is increasingly prescribed. The side effects of metformin are very well known and include digestives symptoms such as diarrhea, digestive disorders, abdominal pain and more rarely LA, known to occur in patients with hypoxemic states such as renal insufficiency, cardiac insufficiency, and septicaemia (Singh, 2014). Even though critical reviews in this field have questioned the supposed dangerousness of LA in metformin-treated patients, the drug's reputation still influences treatment strategies due to the high proportion of patients presenting with contraindications (Lalau et al., 2017). In France, the contraindications are based on the HAS's broad recommendations and on the opinion of an expert committee and not on actual studies ("10irp04_reco_diabete_type_2.pdf," n.d.). Metformin should be discontinued in patients suffering from severe renal impairment [glomerular filtration rate (GFR) < 30mL.min-1] and in any situations in which LA can occur (Lalau, 2010). Furthermore, the contraindications differ from one country to another (Kajbaf et al., 2013).

Currently, non-exceptional cases of serious intoxication leading to death are observed (Bonsignore et al., 2014; Cantrell et al., 2012) Metformin can cause potentially life-threatening metabolic acidosis with increased blood lactate level. Although rare, this condition carries a high risk of mortality and may occur in therapeutic use as well as in acute overdose. Most series report an incidence of 3 to 10 per 100,000 patient-years of metformin-associated lactic acidosis (MALA) (Lalau et al., 2017).

It is in this context of the global epidemic of T2D that we wished to carry out a retrospective study, at Angers Poison Control Center (PCC) from September 1999 to September 2016, of cases of metformin poisoning in the general population in order to describe this population and highlight the main risk factors for severe poisoning.

2. MATERIAL AND METHODS

This observational study was a retrospective review of all cases involving metformin intoxication at Angers PCC University Hospital. The Western France poison centre usually receives reports of a large number of cases of poisoning occurring in four French regions, representing a population of more than 12 million people. A total of 58,000 calls are received each year, and 56% of calls come from doctors (compared to 39% from the general public and 5% from nurses and paramedics).

The PCCs data system is called SICAP (Système d'Information des Centres AntiPoison) and depends on the ANSES (French Agency for Food, Environmental and Occupational Health & Safety).

All cases of metformin intoxication reported between September 1999 and September 2016 were extracted from the PCCs databases as authorized by the French Data Protection Committee (CNIL-Commission Nationale de l'Informatique et des Libertés). The inclusion criterion was defined as exposure to metformin in the population with or without symptoms. To carefully evaluate the severity of metformin intoxication, all cases of co-intoxication with only side effects other than those of metformin were excluded and those with a final diagnosis dismissing a toxic cause.

The data extracted included:

- patient demographic data (age; divided into three age groups: <15 years; 15-75 years and >75 years; sex); the >75 years range was chosen regarding the HAS recommendations ("10irp04_reco_diabete_type_2.pdf," n.d.);
- medical history;
- type of intoxication divided into 4 groups: therapeutic accident [medical accidents due to the hazards and risks that exist when care is provided], medication error [medication error is "an avoidable iatrogenic drug event resulting from unintentional dysfunction in the organization of the patient's therapeutic drug management], self-poisoning and accidental intoxication [lack of risk perception, most of them are young children]);
- the severity of poisoning graded using a standardized scheme called Poison Severity Score (PSS) as follows: none (grade 0), minor (grade 1), moderate (grade 2), severe (grade 3) poisoning. The

PSS takes into account the most severe clinical features (cardiovascular, neurological, metabolic, respiratory symptoms) after follow-up. It provides for qualitative evaluation of morbidity and facilitates comparability of data;

- clinical effect (digestive symptoms, Glasgow Coma Score [GCS], cardiovascular shock [defined by the administration of vasopressors in an emergency or intensive care unit]
- intensive care unit admission;
- treatment (haemodialysis, intubation);
- mortality
- including serial laboratory investigations (pH, lactate, creatinine and metformin concentration). The following outcomes were defined: hyperlactataemia (blood lactate >5mmol/L); acidosis (pH<7.32) according to the PSS, metformin overdose (metformin concentration>5mg.L-1) (McNamara and Isbister, 2015; Singh, 2014) and acute renal failure (creatinaemia>125μmol.L-1) (Srisawat et al., 2010). Lactic acidosis is defined by high blood lactate concentration (>5mmol/L) and decreased blood pH (<7.35).

Mortality, cardiovascular shock and severe gravity according to the PSS were chosen to define severity in order to take an objective look at the overall severity of the records.

The primary endpoint was mortality. Secondary endpoints were severe gravity PSS grade 3 and cardiovascular shock. The covariates considered were age, sex, medical history (T2D, cardiovascular history and chronic renal disease), the type of poisoning (self-poisoning and therapeutic accident) and digestive symptoms (diarrhea and vomiting). These covariates were included in a logistical model to analyse each of the study endpoints.

Statistical analysis

Continuous data was summarized using mean +- SD or median and inter-quartile range, and compared using Mann and Whitney tests. Categorical data was summarize using numbers and percentages and compared using exact Fisher tests.

The factors influencing the severity of poisoning, the risk of cardiovascular shock or the mortality were assessed by multivariate logistic regression models. The possible explanatory factors were a priori selected based on clinical knowledge. The considered factors were age (+-60y), gender, T2D, cardio vascular history, therapeutic accident, diarrhea and vomiting. All the tests were two sided with a type I error set at 5%.

3. RESULTS

From September 1999 to September 2016, 382 cases of metformin poisoning were included. A description of the general characteristics of the population is provided in Table 1.

Average age was 44.7 +- 29.7 years with median of 52 years.

Among these cases, 208 involved women and 174 involved men (sex ratio was 0.83).

Circumstances were known in the 382 cases: 197 cases (51%) involved accidental exposure, with medication error or accidental exposure concerning notably children being the most common cause; 127 cases included suicide attempts (33%) and 58 cases concerned therapeutic accident (15%).

The medical history was known in 353 of 382 cases: 173 patients had T2D and 11 cases had a medical history of chronic renal disease.

These cases were divided according to their severity: 261 cases of "null severity" (grade 0), 40 cases of "mild severity" (grade 1), 14 cases of "moderate severity" (grade 2) and 67 cases of "high severity" (grade 3). We listed 21 deaths in this series.

Medication errors and accidental intoxication together account for more than half of the cases (51%). All these records had no symptom with the exception of 3 cases of minor severity according to the PSS. This is a predominantly paediatric population covering accidental intoxication, with children taking medication belonging to someone else in the family, and a geriatric population for medication error by administration error.

As described, all patients in the therapeutic accident category have T2D and use metformin at the therapeutic dose (between 500 mg/day and 3,000 mg/day). According to the PSS, the cases are mainly severe (90% of them are PSS grade 3). Where the medical history of the records is known, the most commonly found clinical presentation is dehydration worsening over several days (mainly of digestive origin with diarrhea in 35% of cases and vomiting in 41% of cases) resulting in acute renal failure, a common symptom in all these cases of severe poisoning and where metformin was never discontinued or reduced.

Neurological and cardiovascular symptoms were often observed (table 1).

Neurological symptoms included coma (58/382) with Coma Glasgow Scale (CGS) <8 (50/382). Cardiovascular shocks were reported in 51 cases (13%). Lactic acidosis was found in 73 cases (18%).

Digestive symptoms concerned 48 cases of vomiting and 25 cases of diarrhea (12% and 6%). The other significant symptom reported in this series is acute renal failure, representing 20% of the entire series and digestive symptoms.

Table 2 shows a description of fatal cases.

Twenty-one fatal cases were reported. Only two types of intoxication are represented by therapeutic accidents and self-poisoning with respectively 71% and 29% of cases. In these 21 fatal cases, diarrhea was found in 33% and vomiting in 14%. Acute renal failure was observed in 20 cases (95%). Metformin was never reported to have been reduced or discontinued before hospital admission. LA was consistently found in these cases with a high plasma lactate concentration: reported in 17 cases with an average of 16.9mmol.L-1. Plasma metformin testing was reported in 14 cases and was greater than 5 mg/L in 13 cases.

In this series, the concentration of metformin in the blood was tested in 48 cases [0.1 to 236 mg / L]. Of these 48 samples, 47 showed supratherapeutic concentrations (> 1.3 mg/L (Schulz et al., 2012)) and 43 showed toxic concentrations (>5 mg/L (Schulz et al., 2012)). Of these 43 cases, there was 38 cases of high severity including 13 deaths.

Multivariate logistic regressions were calculated for the severity of metformin poisoning.

Table 3 describes the link between death and the main risk factor.

An episode of diarrhea increases the risk of mortality (OR 4.142; $p<0.05$). Therapeutic accident is a main risk factor for mortality (OR 5.519; $p<0.05$).

Table 4 describes the link between cardiovascular shock, severe gravity (PSS grade 3) and significant risk factor of metformin poisoning.

Therapeutic accident is a major risk factor (OR 10.930; $p<0.05$) as an episode of diarrhea (OR 4.894; $p<0.05$) of cardiovascular shock.

Therapeutic accidents (OR 22.636; $p<0.05$) and episode of diarrhoea (OR 7.257; $p<0.05$) increases the risk of severe poisoning (grade 3).

4. DISCUSSION

In our study, the aim was to highlight the main risk factor for metformin intoxication. The inclusion criteria were deliberately extended to metformin intake in four situations (self-poisoning, medication error, accidental intoxication and therapeutic accident) and not only covered MALA, in order to show that metformin therapy could be life-threatening and to determine the risk factors in order to avoid severe clinical situations.

The side effects of metformin, which has been prescribed for over 60 years, are well described and indisputable in terms of digestive symptoms such as abdominal discomfort, vomiting or diarrhea. LA is the most severe side effect. The incidence of LA in patients on metformin therapy called MALA appears to be extremely low, at 3 to 10 per 100,000 patient-years (Lalau et al., 2017), however LA can be fatal when it does occur (10 to 45%) (Lalau and Race, 1999). A recent Cochrane review which included 206 prospective trials, concluded that "there is no evidence from prospective comparative trials or from observational cohort study that

metformin is associated with an increased risk of lactic acidosis if prescribed under the study conditions" (Salpeter et al., 2003).

Most studies have attempted to find a link between LA and metformin. However, few of them focussed on looking for risk factors in severe intoxication involving metformin. Our series of 382 cases has highlighted two major risk factors: therapeutic accident and an episode of diarrhea.

The type of intoxication is also an important key to evaluating severity. Therapeutic accident concerns patient with T2D treated with metformin in whom an acute event occurs. This is a major risk factor for severe poisoning, cardiovascular shock and death. Out of the 21 fatal cases, it represents 71% of intoxications, far ahead of self-poisoning representing 29%. All these cases have an acute renal failure at admission and LA in common. Moreover, metformin was never reduced or withdrawn during the acute event. In cases of therapeutic accident, several situations can explain the development of LA. On the one hand, being diabetic increases the risk of developing LA (DeFronzo et al., 2016). On the other hand, the acute event which is the aggravating factor is often an element precipitating LA such as sepsis, ischemia, hypotension or all situations leading to hypoxemia.

Metformin is renally excreted with a clearance approximately linearly correlated to GFR (Duong et al., 2013). Thus, acute renal failure causes the accumulation of metformin which, from a certain concentration, also aggravates LA. Clearly, MALA occurs when metformin levels are severely elevated (Lalau and Race, 1999). In these therapeutic accident situations, metformin must be discontinued or reduced.

An episode of diarrhea is also a major risk factor for death, cardiovascular shock and clinical severity. Most severe cases have a history of digestive symptoms such as diarrhea, vomiting or both. It is unclear whether these are the cause or consequence of intoxication (Heaf, 2014). The dehydration caused by these symptoms is systematically accompanied by acute renal failure which in turn increases accumulation of metformin. It is possible that a vicious circle sets in, only aggravating the situation and possibly lead to LA (EL-Hennawy et al., 2007).

Kim and al. investigated the clinical profiles of MALA patients and risk factors for MALA from a retrospective study of seven diabetic patients taking metformin between 1995 and 2012. They

highlighted two major risks factors; acute renal failure and old-age. They concluded that renal function must be monitored in elderly T2D patients with underlying diseases and conditions causing renal impairment and starting metformin treatment (Kim et al., 2015). The National Pharmacovigilance Network of the Italian Medicines Agency reviewed cases of MALA over a 10-years period between 2001 and 2011. Their study confirms "that most MALA is associated with an inappropriate use of metformin in patients with risk factors for LA " such as acute renal failure present in 50% of cases and concomitant medications such as non-steroidal anti-inflammatory drugs (RENDA et al., n.d.).

The use and monitoring of metformin treatment still raises questions. The main contraindication is severe chronic kidney disease (CKD), although a recent study published in 2013 proposed dosage guidelines for CKD patients with the following maximum daily doses in relation to creatinine clearance: 3 g (120 mL/min); 2 g (60 mL/min); 1 g (15 mL/min); 500 mg (15 mL/min) (Duong et al., 2013). Likewise, patients with heart failure are now authorized to take this therapy (Heaf and van Biesen, 2011). Prescription rules have been changing rapidly over the last few years and seem to be a source of confusion for practitioners. Establishing clear rules of good practice could prevent this kind of situation. Practitioners should be advised to temporarily withdraw or reduced metformin in the event of digestive symptoms, especially diarrhea.

In conclusion, our study shows that we have to exercise caution with T2D patients treated with metformin presenting with an episode of diarrhea, which is a major risk factor of severe overdose. Despite physicians being well-aware of these rules, there are no clear guidelines as to metformin monitoring.

DISCUSSION ET CONCLUSION

Dans notre étude, l'objectif était de mettre en évidence les principaux facteurs de risque d'intoxication par la metformine. Nous avons délibérément choisi une population large avec pour critère d'inclusion la seule prise de metformine pour mettre en évidence les

situations qui pouvaient entrainer des complications graves allant jusqu'au décès et de permettre aux praticiens d'anticiper.

La metformine est actuellement l'antidiabétique oral le plus utilisé en France et aux États Unis. Il a un rôle central dans le traitement des diabétiques de type 2 car d'une part il est prescrit en première intention après l'échec des mesures hygiéno-diététique et d'autres part il possède plusieurs effets bénéfiques : la stabilisation du poids, le métabolisme lipidique et la réduction des complications macro-vasculaires.

Bien que rare, l'acidose lactique est la complication la plus grave de la metformine car associée à un fort taux de mortalité. Le rôle de la metformine dans son apparition fait régulièrement débat et remet en cause sa potentielle dangerosité.

Actuellement, les contre-indications établies par l'HAS en France sont : une insuffisance rénale chronique avec une clairance inférieure à 30 mL/min ; une affection aigue susceptible d'altérer la fonction rénale telle qu'une déshydratation, un choc, une infection grave.

Ces situations cliniques à risque de complications graves sont en réalité toutes celles amenant à une hypoperfusion tissulaire ou une accumulation de metformine, celle-ci étant exclusivement excrétée par voie rénale.

Dans cette étude, 382 cas d'intoxication avec au moins une prise de metformine ont été rapportés dont 67 cas graves avec 21 décès. Elle a mis en évidence les principaux facteurs de risque de sévérité : la prise de metformine au long cours chez des patients diabétique de type 2 et la présence d'un épisode de diarrhée. Dans les 21 décès, les symptômes digestifs et notamment un épisode de diarrhée sont largement retrouvés et l'insuffisance rénale aigue dans la quasi-totalité des cas (20/21). Ces dossiers ont également en commun que la metformine n'a jamais été suspendue ou arrêtée.

Dans une étude de 2002 publiée dans l'American Medical Association, il a été montré que le risque de complications graves est proche de zéro quand les contre-indications sont respectées. Mais en pratique clinique, elles ne sont toutefois pas respectées dans 14 à 27% des cas (Calabrese et al., 2002).

Notre étude confirme que nous devons faire preuve de prudence chez les patients atteints de diabète de type 2 traités par la metformine présentant un épisode de diarrhée, facteur de risque majeur de complications iatrogéniques. Bien que les médecins connaissent ces règles, il n'existe pas de directives claires sur la surveillance des patients sous metformine.

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LISTE DES TABLEAUX

Table 1 Description of the population: 382 patients; Western France PCC, 1999-2016

Variable	Modality	Population	%
Gender	Male	174	45
	Female	208	54
Age (years)	<15	94	24
	15-75	221	57
	>75	61	15
Medical history	Type-2 diabetes	173	45
	Cardiovascular	116	30
	Chronic renal disease	11	2
	Psychiatric	76	19
	Others	69	18
Type of poisoning	Accidental intoxication	97	25
	Medication error	100	26
	Self-poisoning	127	33
	Therapeutic accident	58	15
Severity	None PSS 0	261	68
	Minor PSS 1	40	10
	Moderate PSS 2	14	3
	Severe PSS 3	67	17
Acute renal failure (creat>125umol.L-1)	-	79	20
Coma	Glasgow score 3-7	50	13
	Glasgow score 8-11	3	1
	Glasgow score 11-14	5	1
	Glasgow score 15	324	84
Digestive	Vomiting	48	12
	Diarrhoea	25	6
Cardiovascular shock	-	51	13
Mortality	-	21	5
pH	>7.32	45	11
	7.32-7.25	11	3
	7.24-7.15	11	3
	<7.15	48	12
Lactataemia (>5mmol.L-1)	-	81	21
Lactic acidosis	-	73	18
Plasmatic metforminaemia present	-	48	12
Plasmatic metforminaemia (>5mg/L)	-	43	11
Intensive unit care admission	-	90	23
Haemodialysis	-	69	18
Intubation	-	47	12

Table 2. Description of the 21 fatal cases; Western France PCC, 1999-2016

Sex	Age (years)	Intoxication method	Digestive symptoms	Creatininaemia (µmol.L-1)	Lactataemia (mmol.L-1)	Metforminaemia (mg/L)	Medical presentation
F	50	TA	Yes	980	-	60	*Diarrhoea over 8 days associated with acute renal failure increased by IEC.*
F	70	TA	No	-	29	146	*Acute renal failure due to pyelonephritis.*
F	57	TA	No	640	30	-	*Clinical deterioration over a few days in a cirrhotic patient.*
M	85	SP	No	-	-	80	*Self-poisoning with metformin leading to death despite haemodialysis.*
M	-	TA	-	500	20	-	*Decompensated cirrhosis with major pleurisy associated with septicaemia (urinary origin) leading to multiple organ failure.*
M	76	TA	-	800	19	16	*No clinical history before intensive care unit admission. Acute renal failure on chronic renal disease leading to acute respiratory distress syndrome (ARDS)*
F	73	SP	-	870	22	57	*Suspected self-poisoning with metformin and tenormin leading to cardiovascular shock in a patient with chronic renal disease.*
M	57	TA	Yes	789	10	-	*Digestive symptoms over several days leading to severe acute renal failure.*
M	65	TA	-	401	16	-	*No clinical history before intensive care unit admission for cardiovascular shock.*
M	78	TA	Yes	360	7.4	13.7	*Back pain treated with NSAID and vomiting over several days*
F	51	TA	Yes	1000	20	71.9	*Digestive symptoms with diarrhoea over a few days.*
F	54	TA	No	-	10	-	*Pneumonitis with severe sepsis over several days*
M	76	TA	No	432	9	39.4	*Cardiac arrest from metformin overdose with major lactic acidosis associated with acute renal failure on chronic renal disease*
M	68	TA	No	632		-	*Weight loss and deterioration in state of health over 3 weeks leading to loss of consciousness at home.*
F	91	TA	Yes	524	12	30.1	*Gastroenteritis with vomiting and diarrhoea over several days leading to acute renal failure*
F	63	TA	No	499	17.2	-	*No clinical history before the patient was found in cardiovascular shock at home by her nurse.*
F	49	TA	Yes	-	-	60	*Major stroke associated with acute renal failure.*
F	79	TA	Yes	550	-	62	*Patient with diarrhoea in the last 2 days found at home in a coma GS<7*
M	72	SP	No	100	8.5	-	*Self-poisoning with metformin and diltiazem in a diabetic patient found unconscious at home*
M	64	SP	No	524	11.8	2.5	*Patient with type-2 diabetes found in a coma GS 5 during hospitalisation in the psychiatric unit.*
F	45	SP	-	-	-	236	*Suspected self-poisoning in a woman find dead at home.*

*TA = Therapeutic accident / **SP = Self-poisoning

Table 3 Link between mortality and the main expected risk factor

Variable	Odds Ratio	[95% Conf. Interval]	p-value
Sex	0.847	[0.305; 2.355]	0.751
Age 60	1.116	[0.326; 3.827]	0.861
T2D	1.048	[0.152; 7.239]	0.962
Cardio vascular history	1.492	[0.398; 5.585]	0.553
Therapeutic accident	5.519	[1.544;19.730]	0.009
Diarrhoea	4.142	[1.053;16.291]	0.042
Vomiting	0.152	[0.028 ;0.825]	0.029

Table 4 Link between cardiovascular shock, severe gravity and the main expected risk factor (results are adjusted on Sex, age +-60y, type II diabetes and cardiovascular history)

Endpoints	Variable	Odds ratio	[95% Conf. Interval]	p-value
Cardiovascular shock	**Therapeutic accident**	**10.930**	**[3.798;31.456]**	**0.000**
	Diarrhoea	**4.894**	**[1.340;17.870]**	**0.016**
	Vomiting	0.808	[0.256; 2.545]	0.715
Severe Gravity ≥PSS3	**Therapeutic accident**	**22.636**	**[7.712;66.442]**	**0.000**
	Diarrhoea	**7.257**	**[1.038;50.753]**	**0.046**
	Vomiting	1.672	[0.484; 5.772]	0.416

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ANNEXES

Annexe 1 Poison Severity Score

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
	0	1	2	3	4
	No symptoms or signs	Mild, transient and spontaneously resolving symptoms or signs	Pronounced or prolonged symptoms or signs	Severe or life-threatening symptoms or signs	Death
GI-tract		- Vomiting, diarrhoea, pain - Irritation, 1st degree burns, minimal ulcerations in the mouth - Endoscopy: erythema, oedema	- Pronounced or prolonged vomiting, diarrhoea, pain, ileus - 1st degree burns of critical localization or 2nd and 3rd degree burns in restricted area - Dysphagia - Endoscopy: ulcerative transmucosal lesions	- Massive haemorrage, perforation - more widespread 2nd and 3rd degree burns - severe dysphagia - Endoscopy: ulcerative transmural lesions, circumferential lesions, perforation	
Respiratory system		- Irritation, coughing, breathlessness, mild dyspnoea, mild bronchospasm - Chest X-ray: abnormal with minor or no symptoms	- Prolonged coughing, bronchospasm, dyspnoea, stridor, hypoxemia requiring extra oxygen - Chest X-ray: abnormal with moderate symptoms	- Manifest respiratory insufficiency (due to e.g. severe bronchospasm, airway obstruction, glottal oedema, pulmonary oedema, ARDS, pneumonitis, pneumonia, pneumothorax)	
Nervous system		- Drowsiness, vertigo, tinnitus, ataxia - Restlessness - Mild extrapyramidal symptoms - Mild cholinergic/anticholinergic symptoms - Paraesthesia - Mild visual or auditory disturbances	- Unconsciousness with appropriate response to pain - Brief apnoea, bradypnoea - Confusion, agitation, hallucinations, delirium - Infrequent, generalized or local seizures - Pronounced extrapyramidal symptoms - Pronounced cholinergic/ anticholinergic symptoms - Localized paralysis not affecting vital functions - Visual and auditory disturbances	- Deep coma with inappopriate response to pain or unresponsive to pain - Respiratory depression with insufficiency - Extreme agitation - Frequent, generalized seizures, status epilepticus, opisthotonus - Generalized paralysis or paralysis affecting vital functions - Blindness, deafness	

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
	0	1	2	3	4
	No symptoms or signs	Mild, transient and spontaneously resolving symptoms or signs	Pronounced or prolonged symptoms or signs	Severe or life-threatening symptoms or signs	Death
Cardio-vascular system		- Isolated extrasystoles - Mild and transient hypo/hypertension	- Sinus bradycardia (HR~40-50 in adults, 60-80 in infants and children, 80-90 in neonates) - Sinus tachycardia (HR~140-180 in adults, 160-190 in infants and children, 160-200 in neonates) - Frequent extrasystoles, atrial fibrillation/flutter, AV-block I-II, prolonged QRS and QTc-time, repolarization abnormalities - Myocardial ischaemia - More pronounced hypo/hypertension	- Severe sinus bradycardia (HR~<40 in adults, <60 in infants and children, <80 in neonates) - Severe sinus tachycardia (HR~>180 in adults, > 190 in infants and children, > 200 in neonates) - Life-threatening ventricular dysrhythmias, AV block III, asystole - Myocardial infarction - Shock, hypertensive crisis	
Metabolic balance		- Mild acid-base disturbances (HCO_3 ~15-20 or 30-40 mmol/l; pH ~7,25-7,32 or 7,50-7,59) - Mild electrolyte and fluid disturbances (K: 3,0-3,4 or 5,2-5,9 mmol/l) - Mild hypoglycaemia (~50-70mg/dl or 2,8-3,9 mmol/l in adults) - Hyperthermia of short duration	- More pronounced acid-base disturbances (HCO_3 ~10-14 or > 40 mmol/l; pH ~7,15-7,24 or 7,60-7,69) - More pronounced electrolyte and fluid disturbances (K: 2,5-2,9 or 6,0-6,9 mmol/l) - More pronounced hypoglycaemia (~30-50mg/dl or 1,7-2,8 mmol/l in adults) - Hyperthermia of longer duration	- Severe acid-base disturbances (HCO_3 ~<10 ; pH ~<7,15 or > 7,7) - Severe electrolyte and fluid disturbances (K: < 2,5 or > 7,0 mmol/l) - Severe hypoglycaemia (~ <30 mg/dl or 1,7 mmol/l in adults) - Dangerous hypo- or hyperthermia	
Liver		- Minimal rise in serum enzymes	- Rise in serum enzymes (ASAT, ALAT ~5-50 x normal) but no diagnostic biochemical (e.g. ammonia, clotting factors) or clinical evidence of liver dysfunction	- Rise in serum enzymes (~>50 x normal) or biochemical (e.g. ammonia, clotting factors) or clinical evidence of liver failure	
Kidney		- Minimal proteinuria/ haematuria	- Massive proteinuria/ haematuria - Renal dysfunction (e.g. oliguria, polyuria, serum creatinine of ~ 200-500 µmol/l)	- Renal failure (e.g. anuria, serum creatinine of > 500 µmol/l)	

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
	0	1	2	3	4
	No symptoms or signs	Mild, transient and spontaneously resolving symptoms or signs	Pronounced or prolonged symptoms or signs	Severe or life-threatening symptoms or signs	Death
Blood		- Mild haemolysis - Mild methaemoglobinemia (metHb ~10-30%)	- Haemolysis - More pronounced methaemoglobinemia (metHb ~30-50%) - Coagulation disturbances without bleeding - Anaemia, leukopenia, thrombocytopenia	- Massive haemolysis - Severe methaemoglobinemia (metHb ~>50%) - Coagulation disturbances with bleeding - Severe anaemia, leukopenia, thrombocytopenia	
Muscular system		- Mild pain, tenderness - CPK ~250-1500 iu/l	- Pain, rigidity, cramping and fasciculation - Rhabdomyolisis, CPK ~1500-10000 iu/l	- Intense pain, extreme rigidity, extensive cramping and fasciculation - Rhabdomyolisis, CPK ~>10000 iu/l - Compartment syndrome	
Local effects on skin		- Irritation, 1st degree burns (reddening) or 2nd degree burns in < 10% of body surface area	- 2nd degree burns in 10-50% of body surface (children: 10-30%) or 3rd degree burns in < 2% of body surface area	- 2nd degree burns in > 50% of body surface (children >30%) or 3rd degree burns in > 2% of body surface area	
Local effects on eye		- Irritation, redness, lacrimation, mild palpebral oedema	- Intense irritation, corneal abrasion - Minor (punctate) corneal ulcers	- Corneal ulcers (other than punctate), perforation - Permanent damage	
Local effects from bites and stings		- Local swelling, itching - Mild pain	- Swelling involving the whole extremity, local necrosis - Moderate pain	- Swelling involving the whole extremity and significant parts of adjacent area, more extensive necrosis - Critical localization of swelling threatening the airways - Extreme pain	

STEVENS Alexandre

Étude descriptive de la sévérité des intoxications à la metformine au Centre Antipoison d'Angers de 1999 à 2016

RÉSUMÉ

Contexte: La prévalence du diabète de type 2 continue d'augmenter dans le monde. La metformine est toujours le gold standard et est de plus en plus prescrit. La surveillance de la metformine continue d'être débattue en raison de son association avec l'acidose lactique, une complication rare mais potentiellement mortelle. L'objectif de cette étude est de décrire l'intoxication par la metformine dans la population générale et de mettre en évidence les principaux facteurs de risque d'intoxications graves.

Méthodes: Étude rétrospective des cas d'intoxication par la metformine de septembre 1999 à septembre 2016 au Centre Antipoison du Centre hospitalier universitaire d'Angers. Le critère principal était la mortalité. Les critères secondaires étaient la gravité sévère (grade 3) et le choc cardiovasculaire.

Résultats: 382 cas d'intoxication par la metformine ont été inclus: 261 cas de «gravité nulle» (grade 0), 40 cas de «sévérité légère» (grade 1), 14 cas de «gravité modérée» (grade 2) et 67 cas de sévérité élevée »(grade 3). Nous avons répertorié 21 décès dans cette série : 71% d'accidents thérapeutiques et 29% d'intoxication médicamenteuses volontaires.
Les accidents thérapeutiques et les épisodes de diarrhée étaient associés à un risque plus élevé de mortalité. Les mêmes facteurs de risque sont retrouvés pour la gravité sévère et le choc cardiovasculaire.

Conclusions: Les patients diabétiques de type 2 traités avec la metformine au long cours peuvent présenter des complications iatrogènes graves. Le suivi de leur traitement doit être pris au sérieux, en particulier en cas de symptômes digestifs tels que la diarrhée.

Mots-clés : Metformine, intoxication, sévérité

Metformin overdose : a serious iatrogenic complication

ABSTRACT

Background: The prevalence of type-2 diabetes continues to rise across the world. Metformin is still the gold standard and is thereby increasingly prescribed. Monitoring of metformin continues to be debated because of its association with lactic acidosis, a rare but life-threatening complication. The aim of this study is to describe metformin poisoning in the general population and to highlight the main risk factor for severe poisoning.

Methods: Retrospective study of metformin poisoning from September 1999 to September 2016 at Angers University Hospital's Poison Control Centre. The primary endpoint was mortality. Secondary endpoints were high gravity (grade 3) and cardiovascular shock.

Results: 382 cases of metformin poisoning were included: 261 cases of "null severity" (grade 0), 40 cases of "mild severity" (grade 1), 14 cases of "moderate severity" (grade 2) and 67 cases of "high severity" (grade 3). We listed 21 deaths in this series: 71% therapeutic accident and 29% self-poisoning.
Circumstance of therapeutic accidents and an episode of diarrhoea were associated with a higher risk of mortality. The same risk factors are found for severe gravity and cardiovascular shock.

Conclusions: Type 2 diabetic patients treated with long-term metformin may experience serious iatrogenic complications. Monitoring of their treatment should be taken seriously especially in the event of digestive symptoms such as diarrhea.

Keywords : Metformin, poisoning, severity