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Glyphosate ingestion causing multiple organ failure: a near-fatal case report

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Summary. A 55 years old man self-presented to our Emergency Department (ED) reporting an attempted suicide by cutting the left forearm veins and ingesting approximately 200 mL of an herbicide (Myrtos®, containing 36% of glyphosate as isopropylamine salt). Laboratory tests showed metabolic acidosis. Hydration with normal saline and alkalinization with sodium bicarbonate was started according to suggestion of the poison control center, since an antidote was unavailable. Cardiorespiratory condition gradually worsened, so that non-invasive positive pressure ventilation (NIPPV) was applied and infusion of fluids was established. Nevertheless, the patient deteriorated and he needed to be transferred to the Intensive Care Unit (ICU), where he underwent orotracheal intubation and invasive mechanical ventilation. Noradrenaline and adrenaline were infused and fluid resuscitation with crystalloids was incremented. An esophagogastroduodenoscopy (EGD) showed diffuse mucosal erosions of upper digestive tract. No signs of visceral perforation were found during ICU stay. In the following days, the clinical conditions improved and a new EGD showed marked improvement of erosive lesions. After 12 days of ICU stay, the patient was extubated and then transferred to the Psychiatric Unit, in good clinical conditions. Gliphosate ingestion is associated with rapid development of multiple organ failure (MOF). Since an effective antidote is unavailable, major attention should be placed to aggressive life-support care and careful monitoring of complications. (www.actabiomedica.it)

Key words: glyphosate; herbicide; isopropylamine; surfactant; poisoning; multiple organ failure

Introduction

Glyphosate is the active compound of up to 750 different nonselective herbicides (1), thus making glyphosate-based herbicides (GlyBH) the most widely commercially available and used herbicides worldwide (2, 3). GlyBH are used on feed crops for cultivation, especially before harvest, and even more intensively for genetically modified plants that are engineered to tolerate this compound (4). Since the biochemical pathway involved in plants death and desiccation is unique and cannot be found in vertebrates, it is hence conventionally assumed that glyphosate may be safe for mammals, including humans (5). This explains the large diffusion of GlyBH among the many commercially available herbicides since the early seventies.

A growing number of GlyBH toxicity reports have been published in the last decades, both regarding low-dose, chronic exposition (6, 7), and high dose ingestion (8-11), which question the fact that assumption or absorption of this compound may be absolutely safe for humans.

Commercial GlyBH formulations range from concentrations of 41% or more, to 1% formulations prevalently marketed for domestic use. All these preparations generally consist of an aqueous mixture of iso-

propylamine salt of glyphosate (i.e., a surfactant), various minor components such as anti-foaming and color agents, along with ionic compounds for pH equilibration (12). The toxic effects of commercial formulations can be explained, at least in part, by GlyBH adjuvants, which have their own toxicity, but may also enhance glyphosate toxicity (3). Overall, it is hence challenging to differentiate the toxicity of glyphosate itself from that of its formulation, and it is even more difficult to define the relative contribution of coformulants to the overall toxicity. Due to such an enormous difference in concentration and co-formulations, data on toxicity are mostly difficult to collect and analyze. Despite the literature information is fairly conflicting, especially regarding chronic expositions, several lines of evidence indicate that GlyBH could be even toxic at concentrations below the lowest regulatory values of exposition (3). The most frequently adverse effects after chronic toxic expositions include teratogenic, tumorigenic and hepato-renal complications, which are sometime detected within the range of recommended acceptable daily intake (3), thus challenging the assumption of GlyBH safety at the widely accepted values which frequently contaminate food and environment.

In this article we describe the case of a massive ingestion of GlyBH for suicidal purpose.

Case report

A 55 years old man self-presented to the Emergency Department (ED) of the University Hospital of Parma on February 12th, 2017, reporting an attempted suicide approximately 3-4 hours before admission, by cutting the left forearm veins. After a couple of superficial and uncomplicated wounds, not involving veins, have been sutured, the patient suddenly started vomiting. Concomitantly, he admitted to have ingested approximately 200 mL of an herbicide (Myrtos®, containing 36% of glyphosate as isopropylamine salt) one hour before the suicide attempt. A thorough clinical evaluation was performed and laboratory investigations were ordered, which included complete blood cell count (CBC), routine blood chemical tests, arterial blood gas (ABG) analysis and electrocardiogram (ECG). Cardiorespiratory parameters were in the normal ranges. Laboratory tests showed metabolic acidosis (Table 1 - ED admission). The corrected QT interval (QTc) was slightly lengthened (450 ms). The poison control center was hence contacted, and confirmed that a specific antidote is unavailable for this herbicide. After hydration with normal saline and alkalinization with sodium bicarbonate was established, and omeprazole (40 mg bolus and 120 mg/day by continuous infusion) was administered, the patient started to develop mild dyspnea, with peripheral blood oxygen saturation (SpO2) of 88% in room air. Oxygen therapy with Ventimask [fraction of inspired oxygen (FiO2) 40%] was started and the SpO2 increased to 95%. However, the cardiorespiratory conditions deteriorated after 30 minutes. The systolic blood pressure (SBP) fell to 95 mmHg, the heart rate (HR) to 110 bpm, and the SpO2 to 89% despite an increased FiO2 to 50%. The dyspnea continued to worsen, and bilateral rales could be heard. The rate of fluid administration was thus increased, and non-invasive pressure support ventilation (NIPPV) was applied in BPAP mode (i.e. bi-level positive pressure ventilation) (see Table 1 for ABG analysis data - ED stay, 3rd hour). At the same time the patient developed acute renal failure [urine output close to 20 ml/h; blood urea nitrogen (BUN), 43 mg/dl; creatinine, 2.5 mg/dl; estimated glomerular filtration rate (eGFR), 28 mL/min]. After a transitory

Table 1. Arterial blood gas analysis results during first day of hospital stay

ABG values	Time		
	ED admission	ED stay (3rd hour)	ICU admission (12th hour)
pH	7.24	7.36	7.16
PaO_2 (mmHg)	72	64.7	133
$PaCO_2$ (mmHg)	40.2	25.5	58
HCO_3^- (mmol/L)	19	13.9	17.2
BE (mmol/L)	-8.2	-9.5	-7.6
Lac (mmol/L)	2.8	1.8	11.1
SpO_2 (%)	95	91	98
Ventilation	Spontaneous	NIPPV-BPAP	IMV
FiO_2 (%)	21	50	80

Legend: PaO_2 = arterial partial pressure of oxygen, $PaCO_2$ = arterial partial pressure of carbon dioxide, BE = base excess, Lac = lactate, SpO_2 = peripheral oxygen saturation, FiO_2 = fraction of inspired oxygen, NIPPV = noninvasive positive pressure ventilation, BPAP = bilevel positive airway pressure, IMV = invasive mechanical ventilation

clinical improvement, the patient further worsened, by developing severe dyspnea and marked agitation, thus needing to be transferred to the Intensive Care Unit (ICU), where orotracheal intubation and invasive mechanical ventilation (IMV) were established. The chest radiographs showed diffuse interstitial edema. Noradrenaline and adrenaline were infused for managing worsening hypotension (SBP 70 mmHg). Fluid resuscitation with crystalloids was also enhanced and a Swan-Ganz catheter was inserted. Cardiac index was high (4.8 L/min/m^2) combined with a low systemic vascular resistance index (700 dynes - sec/cm^{-5}/m^2). Blood lactate (Lac) was 11.1 mmol/L, with a central venous oxygen saturation (ScvO2) of 77.4% (see Table 1 - ICU admission, 12th hour). This clinical picture led to diagnosing a distributive circulatory shock. The esophagogastroduodenoscopy (EGD) showed diffuse mucosal erosions of upper digestive tract, so that total parenteral nutrition (TPN) needed to be started. A computed tomography (CT) scan of chest and abdomen did not show signs of visceral perforation. One day after ICU admission, the patient become febrile, and Meropenem was administered and maintained for 1 week. In the next days, the clinical conditions gradually improved, thus allowing to reduce vasoactive amines dosage, and the renal function normalized. A new EGD, performed after eight days from admission revealed a marked improvement of erosive lesions. Enteral nutrition was initiated and TPN gradually discontinued, to be finally stopped few days afterwards. After 12 days of ICU staying, the patient was extubated and then transferred to the Psychiatric Unit, in good clinical conditions.

Discussion

GlyBH are among the most commonly used herbicides worldwide. Traditionally, they have been considered as minimally toxic for humans, mainly for the considerable difference of plants and mammals metabolism (5, 6, 13). A growing body of evidence, however, demonstrates that the toxicity of GlyBH may not be insignificant in humans.

Glyphosate is never used without its adjuvants (9, 12), which promote and even enhance its herbicidal activity on plants. However, adjuvants are considered inert diluents by the manufacturers, because they are not seen as possible effectors of herbicide activity. As such, at a regulatory level, glyphosate is tested alone on mammalians in "in vivo" toxicological, developmental and reproductive studies.

The differential effects between GlyBH and glyphosate alone have been clearly observed in a number of studies in mammalian species both in vivo and in vitro (14, 15), showing that the overall toxicity is also clearly mediated by the presence of adjuvants. Nevertheless, and rather surprisingly, the current regulation only refers to glyphosate alone, although this compound is never used in pure formulations. The adjuvants composition of different formulations is extremely variable, and the effects of most of these compounds has not been completely tested (3). Some of them are known to be relatively safe (i.e., sorbic acid, pelargonic acid or glycerine), whereas others can be very toxic (ethoxylated adjuvants) or even carcinogenic (e.g., methylparaben, sodium o-phenylphenate, 1,4-dioxane or formaldehyde) (9).

Several factors are associated with mortality in GlyBH poisoning, including some obvious such as age, comorbidities, total amount of compound ingested, shock at presentation, pulmonary infiltration, metabolic acidosis, hyperkalaemia, type of exposition (i.e., suicide attempt vs. accidental ingestion), renal function, oesophageal and laryngeal injury (16). Two additional prognostic tools have recently been included in the toolkit of the emergency physicians, i.e., prolonged corrected QT interval on electrocardiogram (11), and initial blood lactate levels (17), both of which were found to be good predictors of mortality.

The patient described in this case report exhibited mild corrected QT prolongation, as well as mild lactate elevation, at presentation. He survived, after a complex clinical evolution during ICU staying. Overall, the patient had many characteristic features of glyphosate intoxication such as agitation, progressive respiratory failure, impeding circulatory shock, metabolic acidosis (with high blood lactate value) and erosive lesions of digestive tract.

In conclusion, this case report confirms that glyphosate ingestion may be associated with rapid onset of multiple organ failure (MOF). Since an antidote

is currently unavailable, major focus should be placed on aggressive life-support care and careful monitoring of complications.

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