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Using in vitro cholestyramine as an instead of activated charcoal for the treatment of drug poisoning

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Abstract
Worldwide, many cases of drug poisoning occur, filling hospital emergency rooms. The actuality treatments are approached with activated charcoal, except the poisoning for iron. Therefore, this In vitro experimental study will be developed to whose objective will be estimate the adsorption of cholestyramine compared to the adsorption of activated charcoal on acetaminophen, ibuprofen, valproic acid and iron. 8 dissolutions for each of the drugs; and 50 g of activated charcoal will be added and 24 g of cholestyramine. The normal conditions temperature 37 ° C, whit 50 revolutions per minute, the dissolution volume 900 m. Buffer pH 5,8, pH 7,2, pH 7,5 and 0,1 N hydrochloric acid, with a time between 30 and 60 minutes. The samples are filtered and read in UV / visible spectrophotometer at 243, 221, 205 nm and atomic absorption 243 nm. In a 2x2 table the statistics are compared in software Epiinfo. The results reveal that activated charcoal has an adsorption of 99% of acetaminophen, ibuprofen 92%, valproic acid 41% and iron 7%. Cholestyramine an adsorption of 46% of acetaminophen, ibuprofen 91%, valproic acid 71% and iron 2%. There was a significant difference between activated charcoal and cholestyramine in acetaminophen and valproic acid. There was no difference in ibuprofen and iron. Therefore, it is concluded that cholestyramine could be an alternative to treat poisoning by acetaminophen, ibuprofen and valproic acid, excluding iron. Which, could reduce the number of patients in emergency rooms poisoned with some of these drugs.

Keywords: *Activated charcoal, Drug poisoning, Medical emergencies, Medical poisonings, Poisoning treatment, Using cholestyramine.*

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I. INTRODUCTION

Analgesic poisonings are very common, if demonstrated by an investigation carried out from 2005 to 2012 in the United Kingdom, by the Office for National Statistics, relating self-poisoning due to the consumption of analgesics [1]. In the North of Tunisia, during January 2005 and December 2015, 204 cases of suicide occurred, with the most frequent cases due to ingestion of psychotropic and cardiotropic drugs [2]. At the Konya Training and Research Hospital in Turkey it was shown that from January 2010 to February 2013 there was a high frequency of poisoning by antiepileptic drugs, with valproic acid involved [3]. A report from the information center on drugs and poison at the King Khaled University Hospital in Riyadh, Saudi Arabia, revealed that during January 2010 to December 2016 there were 735 children with poisoning by oral ingestion, of which 70% were related to analgesic drugs [4]. The National Poisons Data System in the United States reported from 2007 to 2015, 1,5 million reports of poisonings from pharmaceutical exposures, acetaminophen being involved in an average of 30.000 cases per year, it was also revealed that in in 2016 there were 8.000 cases of valproic acid poisoning [5], [6]. In Colombia, the indiscriminate intake of over-the-counter drugs formulated such as ibuprofen, acetaminophen, ferrous sulfate and valproic acid, has caused some people to consume them without a prescription, which could lead to poisoning and death [7], [8]. In Colombia, the National Institute of Health in its Biweekly Report of National Epidemiology presented 63.177 cases of drug poisoning, ending in deaths of 158 cases between 2008 and 2015 [9]. Cisproquim also revealed in a report from 2012, that in Colombia drug poisonings were the most incidents in the population of minors, acetaminophen being involved [10]. In the epidemiological period III in Colombia in 2016, there were 2.219 cases of drug poisoning, also in 2017 drugs became the main cause of poisoning with 13.372 cases [11], [12]. In the second quarter of 2017 and 2018 in the city of Bogotá there were 1.142 cases of drug intoxication, with acetaminophen being the most prevalent, followed by ibuprofen, valproic acid and iron, with ferrous sulfate being the source of this [13], [14]. In Bucaramanga, in 2018, 3 girls between the ages of 11 and 13 were almost poisoned by consuming acetaminophen in a challenge called acetaminophen, which was viral on social networks [15]. It is also highlighted that in the department of Antioquia in the first semester of 2019 there were 320 cases of drug poisoning [16].

At this time in Colombia and in the world, activated carbon is the only adsorbent used to treat drug poisoning with acetaminophen, ibuprofen and valproic acid in a single dose of 1 gram per Kg of weight orally, if the time elapsed from ingestion is less than 2 hours. However, activated charcoal is not recommended to treat poisonings due to iron intake as it has poor adsorption. [17], [18]. Activated carbon as an adsorbent is the most widely used for drug poisoning since adverse reactions are rare and exceptionally serious. [19]. A descriptive study carried out in the Emergency Service of the Hospital de Barcelona during the years 2001 and 2008, showed that the intoxicated patients treated with activated charcoal as an adsorbent did not present significant adverse reactions [20]. Drug overdose poisonings can be treated with activated charcoal in doses of 1 g / Kg in ages 1 month to 12 years, and doses of 50 g in ages 12 to 18 years, since the administration of activated charcoal 30 minutes after ingestion of the drug can reduce its absorption by 50%, and by 40% if administered 60 minutes later [21].

The oral administration of activated charcoal in suspension at a dose of 1 g / Kg has been shown to reduce the degree of systemic exposure due to paracetamol overdose, since the activated charcoal particles in the suspension are characterized by having a large surface area [22], [23]. Gastrointestinal decontamination with activated charcoal is highly recommended in valproic acid poisoning, as long as the patient presents to the emergency department within 2 hours of ingestion, however, L-carnitine as an antidote for valproic acid poisoning it is also very effective [6]. Hemoperfusion with activated charcoal in valproic acid poisoning patients is considered a good option since it allows the elimination of the drug, improving the patient's recovery [24]. Many non-steroidal anti-inflammatory drugs are highly prescribed and over-the-counter, and they also have different chemical groups that affect their toxicity a bit, such as oxicam (meloxicam, piroxicam and tenoxicam), phenyl propionic (aryl propionic), acid derivatives (fenbufen, ibuprofen, naproxen), tiaprofenic acid and mefenamic acid) and coxib (celecoxib and etoricoxib). However, poisoning from high doses of NSAIDs is treated with activated charcoal one hour after the overdose [25]. The metabolic effects of iron poisoning are proportional to the concentration of free iron, iron is ingested orally in different salts, which may reflect an increase or decrease in plasma. Iron poisoning in patients who have eaten more than 20 micrograms of elemental iron / kg of their body weight should be hospitalized. The use of activated charcoal in iron poisoning is not recommended since it does not adsorb iron, so the use of deferoxamine is recommended, which is a chelating agent used as an antidote, although there is still uncertainty about the optimal dose in individual patients [26], [27]. Cholestyramine is a polymeric resin which is indicated to treat cardiovascular problems, lipid-lowering and bile acid sequestrant. However, it can be observed in the research conducted by [28], how it interacts with some drugs such as: paracetamol, ibuprofen and valproic acid, and as a consequence of such a reaction, she their reducing bioavailability when administered orally.

II. MATERIALS AND METHODOLOGY

The present study is an experimental design that sought to evaluate the role of cholestyramine compared to activated carbon as a possible adsorbent for drugs such as acetaminophen, ibuprofen, valproic acid and iron, which at high doses is considered toxic to humans. For this purpose, the requirements of the Pharmacopoeia of the United States of America USP 40 NF 35 were followed and thus dissolution media were created in the laboratory that emulated the pH of the stomach (between 1 to 2) and the intestine (between 5,6 to 7,5), as is as the peristaltic movements and the body temperature were simulated with the help of dissolution equipment. Subsequently, the percentage adsorbed by cholestyramine and activated carbon was determined by means of an instrumental analysis by UV / visible spectrophotometry and atomic absorption. This methodology will be developed in 9 steps.

Step 1. Determination in vitro adsorption of activated carbon in acetaminophen, ibuprofen, valproic acid and iron. Acetaminophen dissolution in dissolution medium pH 5,8 and activated carbon. 900 mL of dissolution medium pH 5,8 for acetaminophen is transferred to 6 dissolution beakers individually and heated to 37 ° C. 7,5 g of raw material acetaminophen is individually added to the 6 glasses; subsequently 50 g of activated carbon were added. The glasses were shaken for 30 minutes using the paddle dissolution method at 50 rpm, maintaining the temperature at 37 ° C. At the end of 30 minutes, the solutions were filtered with the help of a 22 µm Whatman filter paper, the filtrates were collected and diluted by transferring 1 mL to a 100 mL volumetric flask, making up the volume with dissolution medium. 10 mL of the above solution was transferred to a 100 mL volumetric flask and the volume was made up with dissolution medium. The absorbance of the solutions at 243 nm was examined with the help of a UV / visible spectrophotometer using dissolution medium as calibration blank [29], [30]. Acetaminophen standard solution in dissolution medium pH 5,8 (8,3 µg / mL). 8,3 mg of USP acetaminophen primary standard was transferred to a 100 mL volumetric flask, 50 mL of dissolution medium were added, it was placed in ultrasound for 10 minutes and the volume was made up with dissolution medium. A 1 mL aliquot was transferred to a 10 mL volumetric flask and made up to volume with dissolution medium. The absorbance of the solution at 243 nm was examined with the aid of a UV

spectrophotometer using dissolution medium as calibration blank and the% recovered of acetaminophen was calculated [30].

Step 2. Ibuprofen dissolution in dissolution medium pH 7,2 and activated carbon. 900 mL of dissolution medium was transferred to 6 dissolution beakers individually and heated to 37 ° C. 5 g of raw material ibuprofen individually added to the 6 glasses; subsequently 50 g of activated carbon were added. The glasses were shaken for 60 minutes using the paddle dissolution method at 50 rpm, maintaining the temperature at 37 ° C. At the end of the 60 minutes, the solutions were filtered with the help of a 22 µm Whatman filter paper, the filtrates were collected and diluted by transferring 1 mL to a 100 mL volumetric flask, making up the volume with dissolution medium. 5 mL were transferred to a 25 mL volumetric flask, and the volume was made up with dissolution medium. The absorbance of the solutions was examined at 221 nm with the aid of a UV / visible spectrophotometer using dissolution medium as calibration blank [29], [31]. Ibuprofen standard solution in dissolution medium pH 7,2 (11.1 µg / mL). 11,1 mg of USP ibuprofen primary standard were transferred to a 100 mL volumetric flask, 50 mL of dissolution medium were added, it was placed in ultrasound for 10 minutes and the volume was made up with dissolution medium. 5 mL were transferred to a 50 mL volumetric flask and volume was made up with dissolution medium. The absorbance of the solution was read at 221 nm with the aid of a UV / visible spectrophotometer using dissolution medium as calibration blank and the % recovered of ibuprofen was calculated [31].

Step 3. Dissolution of valproic acid in dissolution medium pH 7,5 and activated carbon. 900 mL of dissolution medium was individually transferred to 6 dissolution beakers and heated to 37 ° C. 6 g of raw material valproic acid were individually added to the 6 vessels. Subsequently, 50 g of activated carbon were added. The glasses were shaken for 60 minutes using the paddle dissolution method at 50 rpm, maintaining the temperature at 37 ° C. At the end of 60 minutes, the solutions were filtered with the help of a 22 µm Whatman filter paper, the filtrates were collected and diluted by transferring 5 mL to a 25 mL volumetric flask, made up to volume with dissolution medium. The absorbance of the solutions at 205 nm was examined with the help of a UV / visible spectrophotometer using dissolution medium as calibration blank [29], [32]. Valproic acid standard solution in dissolution medium pH 7,5 (1.332 µg / mL). 666 mg of primary standard of valproic acid USP were transferred to a 100 mL volumetric flask, 20 mL of diluent solution were added, it was placed in ultrasound for 10 minutes and the volume was made up with diluent solution. 5 mL were transferred to a 25 mL volumetric flask and volume was made up with dissolution medium. The absorbance of the solution was read at 205 nm with the help of a UV spectrophotometer using dissolution medium as a calibration blank and the% recovered of valproic acid was calculated [32].

Step 4. Dissolution of iron in 0,1 N hydrochloric acid and activated carbon. 900 mL of 0,1 N hydrochloric acid was individually transferred to 6 dissolution beakers and heated to 37 ° C. 1.549 mg of raw material ferrous sulfate equivalent to 500 mg of elemental iron were individually added to the 6 vessels; subsequently 50 g of activated carbon was added. The glasses were shaken for 45 minutes using the paddle dissolution method at 50 rpm, and maintaining the temperature at 37 ° C. At the end of 45 minutes, the solutions were filtered using a 22 µm Whatman filter paper, and the filtrates were collected. 2 mL were transferred to a 250 mL volumetric flask and the volume was made up with 0,1 N hydrochloric acid [33]. The absorbances of the sample solution and that of three iron standards, which were at a concentration of 5 ppm, 3 ppm and 1 ppm, were read in an atomic absorption equipment at 248,3 nm using an iron cathode lamp and as 0,1 N hydrochloric acid calibration blank [33]. The percentage of iron recovered was calculated with the aid of a calibration curve made with the iron standards 5 ppm, 3 ppm and 1 ppm.

Step 5. Determination in vitro adsorption of cholestyramine in acetaminophen, ibuprofen, valproic acid and iron. Acetaminophen dissolution in dissolution medium pH 5,8 and cholestyramine: 900 mL of dissolution medium was transferred to 6 dissolution beakers individually and heated to 37 ° C. 7,5 g of acetaminophen raw material is added individually to the 6 glasses; subsequently 24 g of cholestyramine were added to the 6 vessels. The glasses were shaken for 30 minutes using the paddle dissolution method at 50 rpm, maintaining the temperature at 37 ° C. At the end of 30 minutes, the solutions were filtered with the help of a 22 µm Whatman filter paper, the filtrates were collected and diluted by transferring 1 mL to a 100 mL volumetric flask, completing the volume with dissolution medium. 10 mL were transferred to a 100 mL volumetric flask and volume was made up with dissolution medium. The absorbance of the solutions and the acetaminophen standard solution were read in dissolution medium pH 5,8 (8,3 µg / mL) at 243 nm with the aid of a UV / visible spectrophotometer using dissolution medium as calibration blank [29], [30]. The percentage of acetaminophen recovered was calculated.

Step 6. Ibuprofen dissolution in dissolution medium pH 7,2 and cholestyramine. 900 mL of dissolution medium was individually transferred to 6 dissolution beakers and heated to 37 ° C. 7,5 g of raw material ibuprofen was added to the 6 glasses individually; subsequently 24 g of cholestyramine were added to the 6 vessels. The 6 glasses were shaken for 60 minutes using the paddle dissolution method at 50 rpm, and maintaining the temperature at 37 ° C. At the end of 60 minutes, the solutions were filtered with the help of a 22

µm Whatman filter paper, the filtrates were collected and diluted by transferring 1 mL to a 100 mL volumetric flask, making up the volume with dissolution medium. 4 mL were transferred to a 25 mL volumetric flask and volume was made up with dissolution medium. The absorbance of the solutions and the ibuprofen standard solution were read in dissolution medium pH 7,2 (13,3 µg / mL) at 221 nm with the help of a UV / visible spectrophotometer using dissolution medium as calibration blank [29], [31]. The percentage of ibuprofen recovered was calculated.

Step 7. Dissolution of valproic acid in dissolution medium pH 7,5 and cholestyramine. 900 mL of dissolution medium was individually transferred to 6 dissolution beakers and heated to 37 ° C. 6 g of raw material valproic acid were individually added to the 6 vessels; subsequently 24 g of cholestyramine were added to the 6 vessels. The glasses were shaken for 60 minutes using the paddle dissolution method at 50 rpm maintaining the temperature at 37 ° C. At the end of 60 minutes, the solutions were filtered using a 22 µm Whatman filter paper, the filtrates were collected and diluted by transferring 5 mL to a 25 mL volumetric flask, making up the volume with dissolution medium. The absorbance of the solutions and the standard solution of valproic acid in dissolution medium pH 7,5 (1.332 µg / mL) were read at 205 nm with the help of a UV / visible spectrophotometer using dissolution medium as calibration blank [29], [32]. Once this done, it will proceed to calculate the valproic acid recovered percentage

Step 8. The dissolution of iron in 0.1 N hydrochloric acid and cholestyramine, 900 mL of 0.1 N hydrochloric acid will be individually transferred to 6 dissolution beakers and heated at 37 ° C. with 1,549 mg of ferrous sulfate raw material equivalent to 500 mg of elemental iron, which will be individually added to the 6 beakers; subsequently, 24 g of cholestyramine will be added to the 6 beakers. Then, they will be shaken for 45 min using the paddle method at 50 rpm, maintaining the temperature at 37 ° C. Subsequently, at the end of 45 min, solutions should be filtered, using a 22 µm Whatman filter paper, collecting the filtrate, from them, 2 mL will be transferred to a 250 mL volumetric flask and the volume will be completed with 0.1 N hydrochloric acid [33]. The absorbances of dissolutions and that of the three iron standards, will be at a concentration of 5 ppm, 3 ppm and 1 ppm, respectively, will be read in an atomic absorption equipment at a wavelength of 248.3 nm, using a cathode iron lamp and 0.1 N hydrochloric acid as calibration blank [33]. The iron recovered percentage will be calculated with the help of a calibration curve of the iron standards.

Step 9. Using Epiinfo software to compare the adsorption of the Activated carbon versus the Cholestyramine with acetaminophen, ibuprofen, valproic acid and iron. Once the adsorbed averages have been obtained, they will be entered into a 2 x 2 table to demonstrated the statistical dependence. Figure 1 shows the sequence of the methodological matrix.

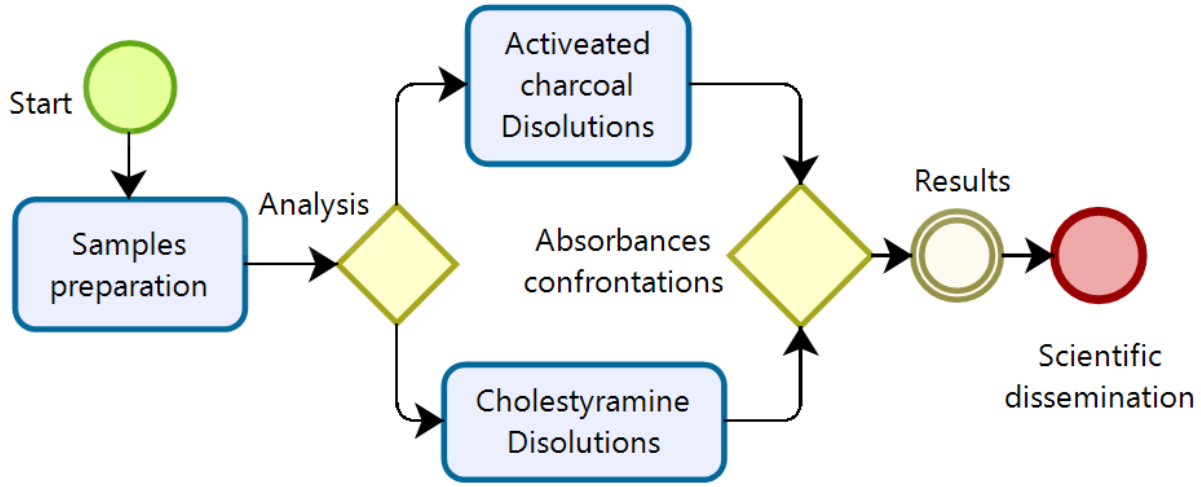

Figure 1: Methodological sequencing flowchart

III. RESULTS AND DISCUSSION

Comparison of dissolution of acetaminophen in dissolution medium pH 5,8 with activated carbon and cholestyramine. Table 1 shows the percentages of acetaminophen that activated carbon and cholestyramine adsorbed in 6 dissolution vessels. The average adsorbed for 6 dissolving vessels was 99% for activated carbon and 46% for cholestyramine. The adsorbed averages were analyzed with the Epiinfo program, resulting in a significant difference between activated carbon as a gold standard and cholestyramine, this was reflected in p = 0,000000.

Table 1: Acetaminophen vs Activated Charcoal and Cholestyramine

Treatment	Acetaminophen + Activated carbon			Acetaminophen + Cholestyramine		
	Weight in mg	% Recovered	% Adsorbed	Weight in mg	% Recovered	% Adsorbed
1	7510.3	1	99	7514	58	42
2	7510.4	1	99	7514	55	45
3	7510.3	1	99	7514	54	46
4	7510.5	1	99	7514.3	54	46
5	7510.4	1	99	7514.2	52	48
6	7510.3	1	99	7514	52	48
Average	7510.37	1	99	7514.08	54	46

Comparison of ibuprofen dissolution in dissolution medium pH 7,2 with activated carbon and cholestyramine. Likewise, tables 3 shows the percentages of ibuprofen adsorbed by activated carbon and cholestyramine in 6 dissolution vessels. The adsorbed average for 6 dissolving vessels was 92% for activated carbon and 91% for cholestyramine, the adsorbed averages were analyzed with the Epiinfo program, resulting in no significant difference between activated carbon as a gold standard and cholestyramine, this was reflected in p = 0,79984261.

Table 2: Ibuprofen vs Activated Charcoal and Cholestyramine

Treatment	Ibuprofen + Activated carbon			Ibuprofen + Cholestyramine		
	Weight in mg	% Recovered	% Adsorbed	Weight in mg	% Recovered	% Adsorbed
1	5010.2	8	92	5030.6	9	91
2	5010	8	92	5030.4	9	91
3	5010.3	8	92	5030.5	9	91
4	5010.2	8	92	5030.2	9	91
5	5010.1	8	92	5030.4	9	91
6	5010.3	8	92	5030.5	9	91
Average	5010.18	8	92	5030.43	9	91

Comparison of dissolution of valproic acid in dissolution medium pH 7,5 with activated carbon and cholestyramine. Other results that we can see are those shown in tables 5 and 6, which show the percentage of valproic acid adsorbed by activated carbon and cholestyramine in 6 dissolution vessels. The average adsorbed for 6 dissolving vessels was 41% for activated carbon and 71% for cholestyramine. The adsorbed averages were analyzed with the Epiinfo program, resulting in a significant difference between activated carbon as a gold standard and cholestyramine, this was reflected in p = 0,00003164. The good adsorption result obtained by cholestyramine is supported, due to the fact that it was able to surpass activated carbon by 30%.

Table 3: Valproic Acid vs Activated Charcoal and Cholestyramine

Treatment	valproic acid + activated carbon			Acetaminophen + Cholestyramine		
	Weight in mg	% Recovered	% Adsorbed	Weight in mg	% Recovered	% Adsorbed
1	6009.3	60	40	6025.3	30	70
2	6009.2	59	41	6025.1	30	70
3	6009.2	59	41	6025.2	29	71
4	6009.3	59	41	6025.1	29	71
5	6009.2	59	41	6025.3	29	71
6	6009.3	59	41	6025.2	29	71
Average	6009.25	59	41	6025.20	29	71

Comparison of iron dissolution in 0,1 N hydrochloric acid dissolution medium with activated carbon and cholestyramine. Figure 1 shows the calibration curve that was made with the standards at different concentrations, revealing an excellent correlation coefficient of 0,99982 that guaranteed the linearity of the

curve. Likewise, table 7 and 8 show the percentage of iron adsorbed by activated carbon and cholestyramine in 6 dissolution vessels. The average adsorbed for 6 dissolving vessels was 7% for activated carbon and 2% for cholestyramine. The adsorbed averages were analyzed with the Epiinfo program, resulting in no significant difference between activated carbon as a gold standard and cholestyramine, this was reflected in p = 0,08810462. The poor adsorption of iron by activated carbon and cholestyramine stands out, despite the fact that there is no significant difference between the two.

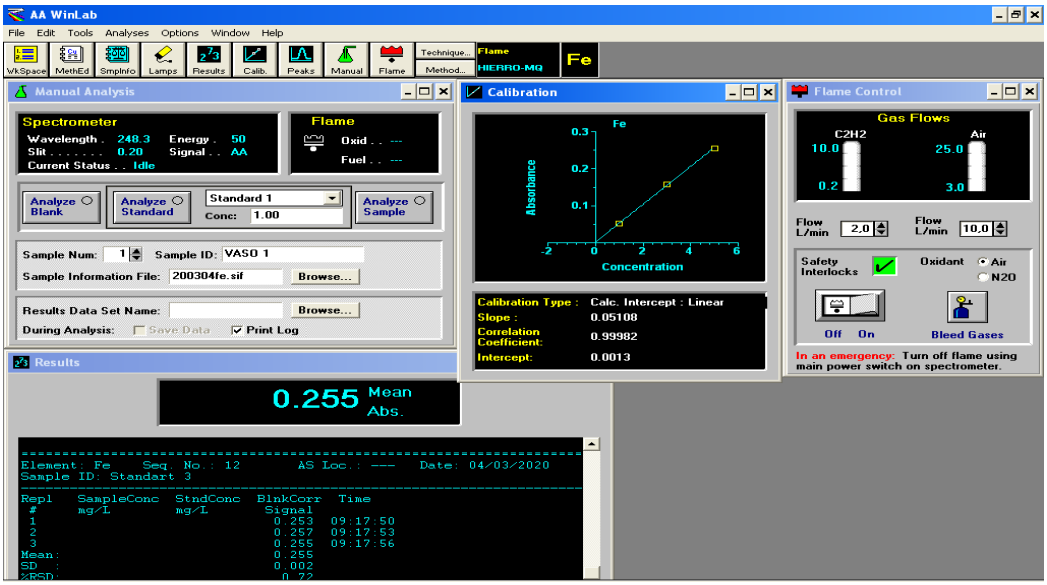

Figure 2. Calibration curve Iron standard 1, 3 and 5 ppm

Table 4: Ferrous Sulfate vs Activated Charcoal

Treatment	Weight in mg ferrous sulfate	Weight in mg as elemental iron	% Iron recovered	% Iron absorbed
1	1.572,2	510,7	93	7
2	1.572,3	510,8	93	7
3	1.572,2	510,7	92	8
4	1.572,5	510,8	92	8
5	1.572,2	510,7	93	7
6	1.572,3	510,8	93	7
Average			93	7

Table 5: Ferrous Sulfate vs Cholestyramine

Treatment	Weight in mg ferrous sulfate	Weight in mg as elemental iron	% Iron recovered	% Iron absorbed
1	1.678,1	545,1	98	2
2	1.678,2	545,2	98	2
3	1.663,3	540,3	99	1
4	1.678,2	545,2	98	2
5	1.662,1	539,9	99	1
6	1.660,2	539,3	99	1
Average			98	2

IV. CONCLUSION

Due to these results, where an in vitro analysis is reported to a comparison between treatment when there is contamination by drugs that use cholestyramine instead of activated charcoal, the Cholestyramine could be an alternative for acetaminophen poisoning, since of a toxic dose of 7.500 mg it was able to adsorb 53%, which is equivalent to 3.517 mg. Cholestyramine could be an option for ibuprofen poisoning, since from a toxic dose of 5.000 mg it was able to adsorb 91%, which is equivalent to 4.550 mg. Cholestyramine could be a candidate for valproic acid poisoning, since from a toxic dose of 6.000 mg it was able to adsorb 71%, which is

equivalent to 4.235 mg. It is also highlighted that cholestyramine adsorbs 30% more valproic acid than activated charcoal, which allows its use in this type of poisoning. Cholestyramine could not be a good choice for iron poisoning, since it is only capable of adsorbing 2% of this metal, highlighting that only 8 mg would be adsorbed from a toxic dose of 500 mg. What is stated by the literature on activated charcoal is confirmed, it should not be used as an adsorbent in poisonings with metals such as iron, since this metal is not capable of adsorbing it. In this experiment, it was possible to show that activated charcoal was only able to adsorb a very poor percentage of 7% of iron in a dose of 500 mg, which is equivalent to 37 mg. This confirms what is stated by the literature on activated charcoal, it should not be used as an adsorbent in iron poisoning, since it is not capable of adsorbing it.

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