Section: General Medicine

Research

ANION GAP AS AN INDICATOR OF ADVERSE OUTCOME IN ACUTE SYNTHETIC PESTICIDE POISONING

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Abstract

Background: Individuals with metabolic acidosis usually experience nausea, vomiting, and fatigue. As the acidosis worsens, the patient begins to feel weak and drowsy. Eventually, blood pressure can become low, leading to shock, coma, and death. These symptoms resemble the toxic symptoms of acute pesticide intoxication. This implies that an acid-base imbalance may aggravate the toxic symptoms or exert a synergistic toxicity with the pesticide itself. The aims & objectives are to observe the effect of the AG on clinical outcome and to determine the composition of the unmeasured anions in acute pesticide intoxication. **Materials and Methods:** A Cross sectional study was conducted among 200 patients admitted in Governmentt medical college, Kottayam with acute pesticide poisoning for a period of 12 months. **Result:** Majority of cases were in the age group 30 to 49 years with a mean age of 46.62 ± 17.98 years. The mean age among high AG was 48.72 ± 17.261 years and in the normal anion group it was 45.13±18.285 years. 137(68%) were males and 63(32%) were females. Among 88 patients with high AG(n=88) 59 were males and 29 were females, among 112 patients with normal AG, there were 78 males and 34 females. Chi square test was done to find out any correlation with gender and AG it was found to be statistically insignificant with a p value of 0.695. Out of 200 patients in the study population 16 patients (8%) had died. With statistical significance it was found that patients with high AG had increased risk of development of intermediate syndrome. All the patients who stayed in the ICU beyond five days had high AG. The mean ICU stay duration in the present study was 4.26 days. The survival time was less among High AG groups compared to normal AG groups and it was statistically significant. **Conclusion:** High Anion Gap at the time of admission in patients with acute synthetic pesticide poisoning can be taken as an indicator of adverse outcome.

INTRODUCTION

The ingestion of pesticides is a common method of suicide in many Asian countries. Patients who have ingested pesticides are candidates for aggressive therapy because their chance for survival improves when adequate therapy is instituted. To provide adequate therapy, it is important to have an in-depth knowledge of clinical markers that can predict the clinical outcome. Patients with acute pesticide intoxication occasionally suffer acid-base imbalanceand high Anion-Gap (high AG) resulting from various causes. Unconsciousness, with or without respiratory failure, is a common clinical manifestation that can lead to respiratory acidosis. Metabolic acidosis is also a common clinical feature of acute pesticide intoxication. Various causes of acute acidosis are encountered in patients with acute pesticide intoxication. First, acute pesticide intoxication is frequently complicated by circulatory collapse, which causes the accumulation of lactic acid which can contribute to anion. Second, additives can provide anions when they enter the body, because the metabolites of some additives are anions: for example, ethylene glycol is commonly included as an antifreeze agent, and its metabolites are glycolic acid or oxalate, and the metabolites of the common solvents methanol and xylene are formaldehyde and formic acid (methanol) and hippuric acid (xylene).

It is important to evaluate the acid-base status and AG in patients with acute pesticide intoxication. In

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Spite of its importance, little is understood about the incidence and effect implicated by the AG on clinical outcome in acute pesticide intoxication. The current study is designed to observe the effect of the AG on clinical outcome and to determine the composition of the unmeasured anions in acute pesticide intoxication.

Objectives

- To assess Anion Gap as an indicator of adverse outcome among patients presenting with acute synthetic pesticide poisoning.
- To study the clinical profile of patients coming to department of general medicine with acute pesticide poisoning
- To explore the association between clinical profile and Anion Gap among these patients.

MATERIALS AND METHODS

After getting permission from SRC, IRB and Department of internal medicine, an informed consent was obtained from the patients enrolled in the study. A cross sectional study was performed to identify the role of AG in the adverse outcome of acute pesticide poisoning. Patients who consumed pesticide and admitted in Govt. medical college Kottayam were included. Study period is 12 months from January 2019 to December 2019.

Sample Size

Sample size is calculated using the formula n=4pq/ d2 Prevalence value is obtained from a study conducted by Lee et al.[1], percentage of patients with high AG who died in acute pesticide poisoning is 44.5%, hence

p=44.5

q= 100-44.5 = 55.5

d= absolute precision (20) = 20% of p = 8.9;

Sample size= 4x44.5x55.5 /8.92 =120

Therefore, a sample size of 200 was selected in the present study.

Inclusion Criteria

All cases of acute synthetic pesticide poisoning admitted in govt medical college Kottayam.

Exclusion criteria

1. All cases of kidney disease
2. Chronic pulmonary diseases
3. Age less than 13 years
4. Patients who present after 24 hrs of consumption of pesticide
5. Patients who consumed alcohol along with poisoning
6. Mixed poisoning
7. Patients who received treatment for acid base imbalance and hemodialysis

Study Procedure

Blood samples for arterial blood gas analysis (ABGA) and electrolytes were drawn simultaneously in the emergency room, before the initiation of treatment. The Anion Gap was noted for every patient. The normal (physiologic) range of the AG is defined as 6-14 mEq/L, and an AG >14.1 mEq/L is considered high. The standard of ABG analysis machine followed was that in the biochemistry lab. The patients were divided into two groups as one with high AG and the other with normal AG according to the value obtained.

The parameters for assessing clinical outcome include the death rate, length of hospital stay (days), length of intensive care unit (ICU) stay (days), and developments of any complications, ventilator need.

Data Management and Statistical Analysis

All the data collected were coded and entered in a Microsoft-Excel sheet which were rechecked and analysed using SPSS statistical software version 18. Quantitative variables were presented as mean and standard deviation. Categorical variables were summarized using frequency and percentage. Statistical testing of association of various factors was done using Pearson Chi square test, independent sample t test and ANOVA. p value less than 0.05 was considered as statistically significant.

RESULTS

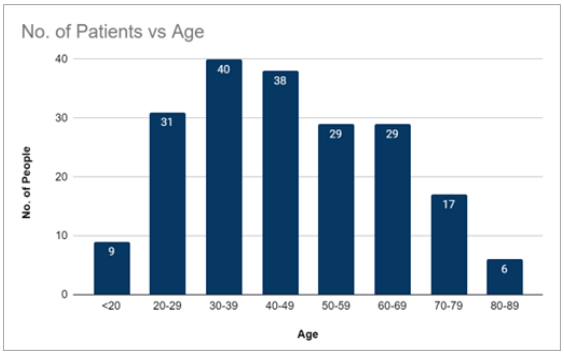

Figure 1: Age distribution of study population

The mean age of patients in this study was 46.62±17.98 years. and most of them were between age 30 to 49 years.

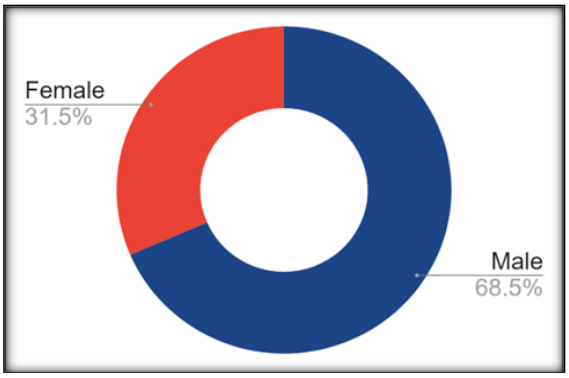

Figure 2: Sex distribution of study population

Out of 200 patients enrolled in the study, 137 (68.5%) were males and 63 (31.5%) were females.

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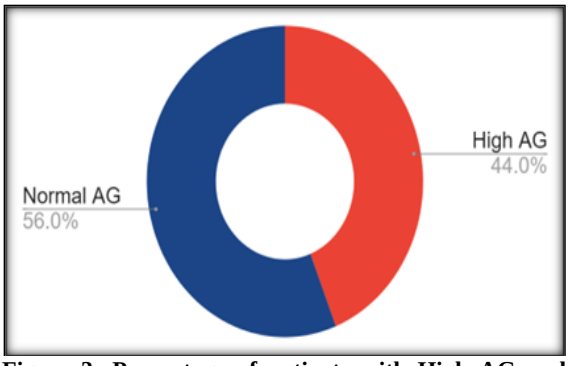

Figure 3: Percentage of patients with High AG and Normal AG

Among the 200 patients enrolled for the study, 112(56%) had normal AG and 88(44%) had High AG.

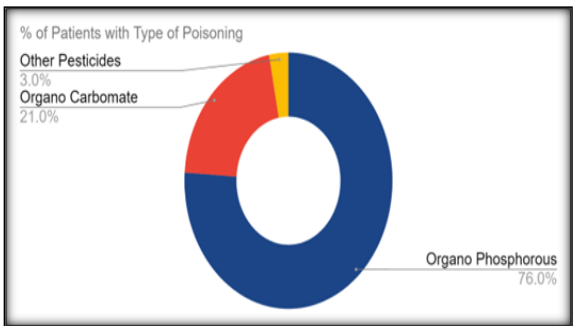

Figure 4: Percentage of patients with different type of poisoning

Among the 200 patients enrolled for the study, 152 (76%) had Organophosphorus poisoning, 42 (21%) had carbamate poisoning and 6 (3%) other pesticide poisoning.

Clinical Features

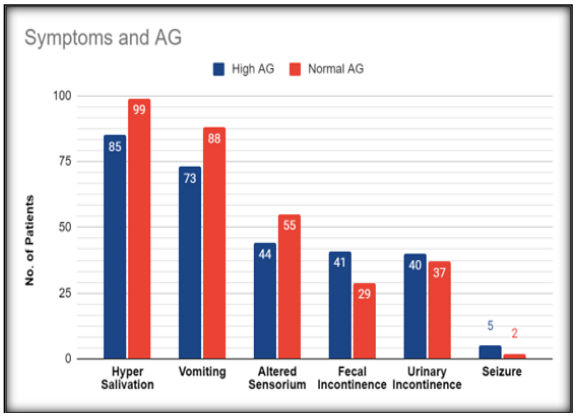

Figure 5: Symptomatology and anion gap

The most common symptom was hypersalivation (184/200) followed by vomiting (161/200). The least common symptom was seizure in the study population. Only fecal incontinence had a significant difference between high and normal anion gap.

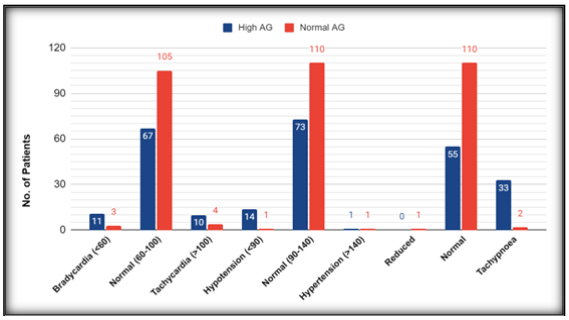

Figure 6: Vitals and Anion Gap

In the study population 14 patients had bradycardia, of which 11 had high AG while 3 had normal AG. There was a statistically significant difference between high and normal AG and bradycardia was associated with high AG. Out of the 15 patientswith hypotension majority of them(14) had high AG and the difference was statistically significant. 35 patients had tachypnea at the time of presentation and most of them (33) were having high AG and the difference was statistically significant between the two groups.

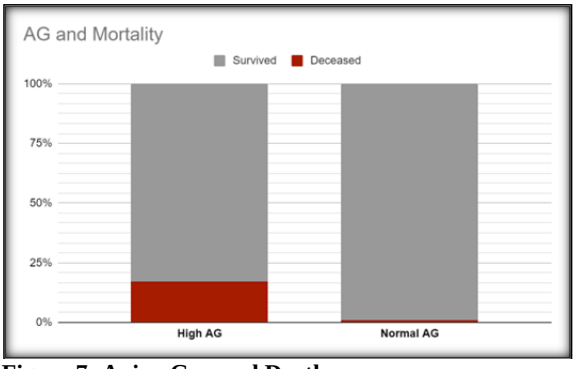

Figure 7: Anion Gap and Death

Among 16 patients who died, 15 patients (94% of death) had high AG and only 1 patient (6%) had normal AG.

Among the patients with High AG (88 (44% of total patients)), 17% were deceased and 83% survived. Among the patients with Normal AG, 0.9% were deceased and 99% were survived. This result indicated that high AG was more commonly seen in patients with poor survival rate.

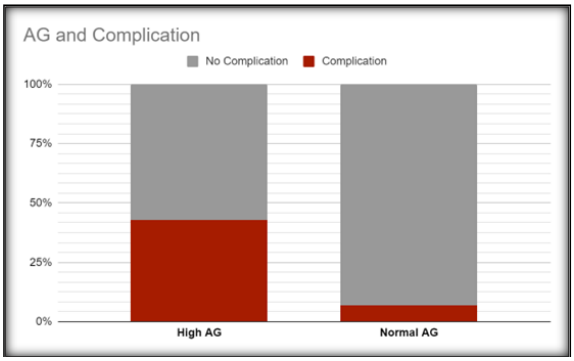

Figure: Anion Gap and complications

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Among the patients with High AG (88 (44% of total patients)), 43% had complications and 57% had less complications. Among the patients with Normal AG, 7% had complications and 93% had less complications. So, with statistical f significance it may be concluded that high AG may be associated with increased risk of development of complications.

Table 1: Mean Age in High-AG And Normal-AG group

	N	Age (years)				
		Range	Min	Max	Mean	Std. Deviation
High-AG	88	69	18	87	48.72	17.261
Normal-AG	112	71	16	87	45.13	18.285

The mean age in high AG group was 48.72 years and in normal AG group was 45.13 years (p=0.160, not significant).

Table 2: Gender distribution in High-AG And Normal-AG

AG		Frequency	Percentage
High AG	Male	59	67.0
	Female	29	33.0
	Total	88	100.0
Normal AG	Male	78	69.6
	Female	34	30.4
	Total	112	100.0

In the high AG group (n=88) 59 were males and 29 were females. Normal AG group had 78 males and 34 females. Chi square test was done to find out any correlation with gender and AG it was found to be statistically insignificant with a p value of 0.695.

Table 3: Different Complications in the study population

Complication	Frequency
Respiratory complications	43
Critical Illness Neuropathy	2

In the study population, 45 patients had at least one complication of which 43 patients had respiratory complications including VAP while 2 patients had Critical illness neuropathy. Many patients had more than one complication.

Table 4: Hospital stay duration in survived with High AG and Normal AG

Duration of Hospital Stay in Survived (Days)	High AG	Normal AG
<5	0	0
5-9	1	38
10-14	6	52
15-19	51	19
20-24	16	1
>30	0	0

Among the 200 patients enrolled for the study184 patients had survived and they stayed for a mean duration of 14.1 days in the hospital.

Table 5: Hospital stay duration in survived patients with Anion Gap (Levene's Test)

	N (survivors)	Mean	Std. Deviation
High AG	73	18.05	2.901
Normal AG	111	11.46	3.479

The observed difference in mean duration of stay among survivors (184/200) in the two AG groups is significant (t = 13.9, mean difference 6.5 (5.6-7.5); p=<0.001). Out of 88 patients with high AG 73 got discharged with a mean hospital stay duration of 18.05 days while patients with normal AG (111/112) had a mean hospital stay of 11.46 days. With high significance (p<0.001) it may be concluded that high AG may lead to longer hospital stay as compared to the patient with normal AG among survivors.

Duration of Stay in Patients who Died

(Kaplan - Meier Survival Analysis)

Table 6: Anion gap and death

AG	Total N	No. of Death
High AG	88	15
Normal AG	112	1
Total	200	16

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Table 7: Hospital stay duration in deceased

	Mean Duration (in Days)
High AG	20.703
Normal AG	23.830
Overall	22.379
Log rank test is significant, p=<0.001	

Kaplan-Meier survival analysis was performed with duration of hospital stay among the dead. The survival time was less among High AG groups compared to normal AG groups and it was statistically significant.

DISCUSSION

In this cross-sectional study, Anion Gap of the patients were analysed at the time of admission along with history taking and clinical examination. Majority of cases were in the age group 30 to 49 years with a mean age of 46.62 ± 17.98 years in the present study. The mean age among high AG was 48.72 ± 17.261 years and in the normal anion group it was 45.13±18.285 years. In the study by Lee et al,[1] the study included 668 male and 390 female patients, with a mean age of 56.8 ± 15.8 years.This shows that the age group of the present study is comparable with their study.The age group selected for the study excluded paediatric age groups. When an independent sample test was done to find out any significant difference with age between high AG and normal AG group it was found to be insignificant.

Gender Distribution

Out of 200 patients enrolled in the study, 137(68%) were males and 63 (32%) were females. Among 88 patients with high AG(n=88) 59 were males and 29 were females, among 112 patients with normal AG, there were 78 males and 34 females. Chi square test was done to find out any correlation with gender and AG it was found to be statistically insignificant with a p value of 0.695. In the study byLee et al,[1] also gender was not statistically significant among deceased and survivors of pesticide poisoning conducted in 2016.

In the present study males were more than females. Vishwanathan and Shrinivasan (1962),[2] reported higher number of suicidal cases among females than males. While Mutalik (1962).[3] Gupta and Patel (1968),[4] Mehta (1971),[5] Balani (1968),[6] and Goel et al (1998),[7] reported higher numbers of males patients. The male predominance in the study indicates the easier accessibility of organophosphorus compounds to them.

Marital Status

Out of 200 patients enrolled in the study, 77% were married and 23% were unmarried.

AG in the Study Population

In the present study 88 patients (46 %) had high AG and 112 patients (54%) were in the normal AG group. In Lee et al,[1] study 45.5% (481/1,058 cases) had high AG, 36.5% 36.6% (387/1,058) had normal AGs and 18 % 18.0% (190/1,058) had low AG. No of patients in the present study and in the study conducted by Lee et al,[1] with high AG show similar distribution in both the studies.

Clinical Profile

In the study population 184/200 (92%) had hypersalivation, 161/200 (80%) patient had vomiting, 99/200 (49.5%) had altered sensorium, 77/200 (38.5%) had urinary incontinence,70/200 (35%) had fecal incontinence, 7/200 (3.5%) had convulsions on presentation. In the study population the most common clinical presentation was hypersalivation followed by vomiting and the least common symptom was seizure. Among these, only fecal incontinence had association with AG statistically. Fecal incontinence was more likely to be associated with high AG.

In this observation bradycardia and tachycardia were more with high AG group. But statistical difference was significantly seen with bradycardia and not with tachycardia. Effect of atropine can be a confounding factor in tachycardia as many of the patients had received atropine from the local hospital. Out of the 15 patientswith hypotension in the study population majority of them (14) had high AG. It was statistically associated with high AG with significance. Thus a patient with high AG is more likely to be associated with hypotension. 35 patients had tachypnea at the time of presentation and most of them (33) were having high AG. It was observed that tachypnoea was associated with a high AG.

According to study in 2011 by Muhammed et al,[8] 50 (16.66%) patients developed episodic convulsions, while in the present study only 3.5% had convulsions. Muhammed et al,[8] also noted thattwenty (6.66%) patients in their study developed profuse diarrhea, but in the present study 35% of patients had diarrhea. Muhammed et al,[8] reported severe bradycardia in 30 (10%) patients in their study and in the present study 14 patients (7%) had bradycardia. Acetylcholinesterase inhibitors when consumed due to parasympathetic activity bradycardia occurs along with other parasympathetic features. In Muhammed et al,[8] 2011 hypotension was seen in 30 (10%) patients, in the present study 15 (7.5%) patients had hypotension which is comparable in both the studiesand majority of them (14 patients) had high AG in the present study which was statistically significant.

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Time of Stomach Wash

25 patients received stomach wash within 4 hours of consumption of pesticide and 175 patients received stomach wash after 4 hours of consumption. There was no significant relation between time of stomach wash and AG in the present study.

Mortality: Out of 200 patients in the study population 16 patients (8%) had died. According to the study by Muhammed et. Al,[8] 50 (16.66%) patients died of different complications of organophosphate poisoning. Among the patients with High AG (88, 44% of total patients), 17% were deceased and 83% were survived. Among the patients with Normal AG, 0.9% were deceased and 99% were survived. This result indicated that high AG was more commonly seen in patients with poor survival rate. In Lee et al,[1] study the mortality was 44.5% among high AG and 19 % was the mortality among normal AG and high AG was associated with increased mortality. Both the study showed that high AG is associated with increased mortality.

Ventilatory Support: In the present study out of 200 patients 33 patients (16.5%) were supported with ventilation. According to Goel et al, in their study, of 103 patients, 36(34.95%) required assisted ventilation. The difference may be due to the difference in the study population. Among the patients with High AG (88 (44% of total patients)), 34% were supported with ventilators and 66% were not supported with ventilators. Among the patients with Normal AG, only 3% were supported with ventilator and 97% were not supported with ventilator. When Chi square test was done to find out the association it was found that the patients with high AG had increased requirement of ventilatory support.

Intermediate Syndrome: In the study population of 200, 12 patients had intermediate syndrome (6%). Among the patients with High AG (88 (44% of total patients)), 15% had Intermediate Syndrome and 85% had no Intermediate Syndrome. Among the patients with Normal AG, no one had Intermediate Syndrome. With statistical significance it was found that patients with high AG had increased risk of development of intermediate syndrome. In the study conducted by Karalliedde and Senanayake,[9] observed an incidence of intermediate syndrome as 11% (10 out of 92 patients) among OP poisoning. It is comparable with our study group.

Complications: Among the patients with High AG (88 (44% of total patients)), 43% had complications and 57% had less complications. Among the patients with Normal AG, 7% had complications and 93% had less complications. So, it may be concluded with statistical significance that patients with high AG are more prone for complications like respiratory complications including VAP and critical illness neuropathy. In the study population, 45 patients had at least one complication of which 43 had respiratory complications including VAP while 2 patients had Critical illness neuropathy. Many patients had more than one complication. Respiratory failure was the commonest complication which may develop within 24hours after exposure.[10-12] Early onset of respiratory failure is due to cholinergic over activity while late onset respiratory failure has been attributed to respiratory infections.

Duration of Hospital Stay: Among the 200 patients enrolled for the study184patients had survived and they stayed for a mean duration of 14.1 daysin the hospital. The observed difference in mean duration of stay among survivors in the High AG and normal AG is significant. Out of 88 patients with high AG 73 got discharged with a mean hospital stay duration of18.05 days. Among survivors with normal AG(111/112) had a mean hospital stay of 11.46 days. In the study conducted by Lee et al,[1] the total hospital stay duration among survivors was 9.9 days which is comparable with the present study. In the present study with high significance ($p<0.001$) it may be concluded that high AG may lead to longer hospital stay as compared to the patient with normal AG among survivors.

ICU Admission: In the study population 42 patients were admitted in the ICU. Among the patients with High AG (88 (44% of total patients)), 37(43%) were admitted in ICU and51(57%) were not admitted in the ICU. Among the patients with Normal AG (112/200),5(4%) had admission in ICU and 107 (96%) were not admitted in the ICU. So, patients with high AG are more prone for increased ICU admissions with statistical significance.

ICU Stay Duration:

In the observation out of 42 patients admitted in the ICU 37 patients were having high AG and most of them (26) stayed less than 5 days. All patients with normal AG who are admitted in ICU (5/42 patients in ICU) had stayed in the ICU less than five days All the patients who stayed in the ICU beyond five days had high AG. The mean ICU stay duration in the present study was 4.26 days.

The mean ICU stay duration among high AG groups was 4.37 days among patients with high AG and 3.25 days among normal AG groups in the present study. ICU stay duration had no association with AG statistically in the present study. In the study conducted by Lee et al,[1] the mean duration of ICU stay was 5.9 days which is comparable with the present study.

Hospital Stay Duration Among Deceased Patients: The mean hospital stay duration in deceased patients is 22.37 days. The mean hospital stay duration of deceased patients in high AG group is 20.7 days and that of normal AG group is 23.8 days. Kaplan -Meier survival analysis was done with duration of hospital stay among dead patients. The survival time was less among High AG groups compared to normal AG groups and it was statistically significant.

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CONCLUSION

Patients with high Anion Gap had increased use of ventilatory support, intensive care, long duration of hospital stay in survivors, increased risk of development of intermediate syndrome and other complications, less survival time among deceased. High anion gap was also associated with increased mortality in acute pesticide poisoning.

The most common clinical feature was hypersalivation followed by vomiting and the least common presentation was seizure. But only Fecal incontinence showed statistical significance with high anion gap. Bradycardia, hypotension and tachypnoea were associated with high anion gap with statistical significance.

High Anion Gap did not show any association with duration of ICU stay and time of stomach wash.

Therefore, it may be concluded that High Anion Gap at the time of admission in patients with acute synthetic pesticide poisoning can be taken as an indicator of adverse outcome.

Limitations

The amount taken could not be properly assessed in most of the cases hence the effect of quantity on anion gap was not properly studied. The exact proportion of additives and the type of additives could not be studied as the details were not available with the subjects and that can be a confounder which can affect the change in Anion Gap. Since the study was a cross sectional study, the delayed complications of the study population could not be studied.

REFERENCES

1. Lee SH, Park S, Lee JW, Hwang IW, Moon HJ, Kim KH, Park SY, Gil HW, Hong SY. The AG is a predictive clinical marker for death in patients with acute pesticide intoxication. Journal of Korean medical science. 2016 Jul 1;31(7):1150-9.
2. Vishwanathan et al: Poisoning by Bug Poison JIMA. 1962;39:345
3. Mutalik GS, Wadia RS and Pai VR. Poisoning by diazinon an organophosphorous insecticide. Journal Of Indian medical association 1962; 38:67-71.
4. Gupta OP. Patel DD. Diazinon Poisoning. Study of 60 cases. JAPI 1968;16:457-463. 73
5. Mehta AB, Shach AC, Joshi LG, Kale AK, Vora DD. Clinical features and plasma cholinesterases activity in poisoning with insecticidal organophosphorous compounds. JAPI 197;19:181.
6. Balani SG et al. Diazinon poisoning. A report of 100 cases with particular references to evaluation of treatment. J A P I 1968;16:911-917.
7. Goel A,Joseph S, Dutta TK.J Assoc Physicians India. Organophosphate poisoning: predicting the need for ventilator support. 1998 sept;46(9)786-90
8. Faiz, Muhammad Saleem, Shaheen Mughal, and Abdul QayoomMemon. "Acute and late complications of organophosphate poisoning." J Coll Physicians Surg Pak 21.5 (2011): 288-90.
9. Karalliedde L, Senanayake N. Acute organophosphorous insecticide poisoning in Sri Lanka. Forensic Science International 1988; 36: 97-100
10. Wren C, Caron PHM, Sendercon JM. Organophosphorous poisoning and complete heart block. Journal of Royal Society of Medicine 1981;74:688-89
11. Tsao TC, Juang YC, Lan RS, Shieh WB, Lee CH. Respiratory failure of acute organophosphate and carbamate poisoning. Chest 1990;98(3):631-6
12. Baroff RB, Fenichel GM, C David Marsden-Buttex worth Heinemann. Neurology in clinical practice – principles of diagnosis and management. Bradly WG, edt. vol. II, 3rd edn. 2000:p.1514-1515.

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