ORIGINAL RESEARCH PAPER

Volume-8 | Issue-3 | March-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

**SUCCESSFUL OUTCOMES IN RODENTICIDE POISONING CONTAINING YELLOW PHOSPHORUS PASTE AND ZINC PHOSPHIDE BY VITAMIN K, EARLY PLASMAPHERESIS & L-ORNITHINE-L-ASPARTATE.

General Medicine

Dr Deepa Banjan*	MD, Associate Professor Department of Medicine. RGMC & CSMH Kalwa *Corresponding Author
Dr Jyotsna Zope	DM, Department of Nephrology Mukta Dialysis centre. RGMC & CSMH.
Dr Sandhya Khadse	MD, Paediatrics
Dr Parmesh Wanga	MD, Department of Medicine.
Dr Shankar Bhanushali	MD, Department of Medicine.
Dr Amitanshu Hazare	Department of Medicine.
Dr Balwant Chavhan	Department of Medicine.
Dr Sachin Shinde	Department of Medicine.

ABSTRACT

Yellow phosphorus paste with 3 % phosphorus YP, is commonly used as a Rodenticide in India. YP is a Severe local and protoplasmic toxin causing damage to gastrointestinal, hepatic, cardiovascular, and renal systems. Paste consumption symptoms are different from direct exposure to yellow phosphorus used in industries. 3% paste is often used as a suicidal drug due to its easy availability1. Fulminant hepatic failure and severe coagulopathy leads to death in untreated or late treated cases .27% mortality has been reported in phosphorus intoxication due to use firework manufacturing 3,4. The Authors present observations of symptoms, signs, investigations caused due to rodenticide containing YP and Zinc phosphide. The study also proposes diagnostic criteria based on INR ratio, platelet count and prothrombin time for early therapeutic intervention. 90 %Patients with signs of early signs of coagulopathy and deranged prothrombin time showed complete recovery from complications. Early Plasmapheresis for recovery worked best when PT INR was between 1.17-1.63. Till date only Liver transplants had been advocated as the final treatment of fulminant liver failure occurring as complication of rodenticide poisoning. The Authors concur that symptoms due to paste/powder forms of rodenticide phosphorus compounds differ from elemental phosphorus of industrial use.10 Phytomenedione and not any other form of drug is recommended. The study proposes role of a possible immune mediated autoantibody response in patients who had consumed YP/ZP. The dramatic response to plasmapheresis makes the authors propose an autoimmune/ antigenic origin in patients suffering complications due to YP/ZP without LD consumption or accidental exposure.

KEYWORDS

Yellow Phosphorus paste, Zinc phosphide powder, Plasmapheresis, Haemodialysis, Liver cell failure, Rodenticide, L-ornithine-L- aspartate.

INTRODUCTION

Phosphorus is naturally present in organic, inorganic and ionic form in the human body. The measurement of ionic form is possible by laboratory diagnosis in vivo. Most phosphorus exists as phosphate and intracellular. Orally ingested organic form of Phosphorus can be lethal to living cells without causing pain, hence it is a popular painless rodenticide. Unfortunately, it's easy availability and accessibility in household use, also has made it a cheap suicidal drug. The lethal dose of oral phosphorus can be as minimal as 0.2mg/kg. 18 cases of oral consumption of Phosphorus with suicidal intent were reported by Siddhartha et all [4]. Symptoms and signs of yellow phosphorus intoxication are immediate and delayed. The immediate toxic signs include: Gastrointestinal discomfort, Vomiting, Jaundice, Bleeding from various sites, breathlessness. [ref] Sudden deaths have been reported if taken along with alcohol. [ref] Late complications include development of fossy Jaw. [ref] Signs are seen in first 6-8 hours of consumption, if untreated, death occurs due to coagulopathy, internal bleeding and fulminant Liver cell failure in 24-72 hrs. [16 P-63-70]. Signs of yellow phosphorus paste consumption differ from acute toxicity due to exposure to elemental Yellow phosphorus and should not be confused.[2] In this observational retrospective analytical study conducted in a teaching Hospital over 1 year, The Authors have presented the symptoms, signs, investigations, diagnostic criteria for impending complications and successful treatment modalities for rodenticide containing Yellow phosphorus & Zinc Phosphide paste. Mortality has been reported in paste form consumption too making it a lethal systemic poison. The authors also strongly concur with the statement that zinc phosphide and elemental yellow phosphorus paste toxicity have different clinical signs and symptoms of presentation than elemental yellow phosphorus in elemental form and application of same diagnostic criteria to different compounds, will result in diagnostic and management errors.[10]

METHODS AND MATERIALS

The retrospective analysis of cases, who has consumed 3 % yellow phosphorus or zinc phosphide rodenticide with suicidal intent, were selected for study over 1 year, After permissions to access data. Medical Case records of symptoms, signs, treatments, complications and outcomes were tabulated. Only registered Cases with complete medical records of history and investigations Cases who left against medical advice were not included. There were no Minors, children, pre-existing hepatic disorders or coagulation profile deranged patients. pregnant mothers were excluded.,

Findings were tabulated in percentage and observational forms. [Table 1,2,3] Serial analysis of Prothrombin time, PT ratio and INR were tabulated for observations. Standard liver function tests coupled with criteria for liver cell failure and coagulopathy were recoded for diagnosing liver cell failure and coagulopathy. Arterial blood gasses, CBC, Platelets X-ray chests, Pre-and post-plasmapheresis. Blood grouping and cross Matching, Prothrombin time with control, INR ratios, Serum Electrolytes, Serum Phosphorus levels, Arterial blood gases, Serum Creatinine, BUN, Urine routine, Stool for Occult blood, Ecg, Coombs tests, Ultrasonography findings were not included for analysis. Interesting photographs kept as departmental records showing serial changes in plasma colour after filtration, recorded [pic 3,4,5,6]. With

consents, were selected for analysis. A comparative analysis with untreated cases showed significant statistical difference in outcomes with cases who had been subjected to IV vitamin k [Phytomenedion], Ornithine-L aspartate & plasmapheresis in rodenticide consumption and untreated cases. Data analysis had statistical significance in outcomes of patients given plasmapheresis Vs untreated as the sample size of cases was less. [p = 0.01, p=0.004 diff = 0.006 with degree of freedom=2]. Recordings were done on excel sheets. Since sample size was small, the 95 %confidence interval was applied to the data and not standard Statistical packages or Annova software.

Observations & conclusions

Table 1 symptoms of presentation.

SR NO	VOMITING	ABDOMINAL PAIN	ICTERUS	OLIGURIA	BREATHLESSNESS	MENTAL IRRITATION	CONSTIPATION	OUTCOME	INDOOR DAYS
1]	Yes 2	Yes	nil	nil	nil	Yes	Yes 3	disch	10
2	Yes 1	Yes	Nil	Nil	Yes	Nil	Yes 3	death	6
3]	Yes 3	YES	YES -3	NIL	NO	nil	Yes 3	disch	7
4	Yes 7	YES	Yes 3	YES 3	NO	nil	Yes 3	disch	17
5	Yes 3	YES	Yes 3	NIL	NO	nil	Yes 2	disch	8
6	Yes 2	YES	Yes 3	NIL	NO	nil	Yes 2	disch	7
7	Yes 2	YES	Nil	NIL	NO	Nil	Yes 1	death	1
8	Yes 3	YES	nil	NIL	NO	Nil	Yes 3	death	3
9	Yes 1	YES	Nil	NIL	Yes terminal event	Yes terminal	Yes 1	death	3
10	Yes 2	YES	Yes 1	NIL	NIL		Yes 3	Dishc	7
11	=2.6 yes	2.6 yes	2.6 days present. Nil	Nil Nil	Nil	Nil	M 2.4 DAYS No	Death	M=7 7

All patients commonly presented with vomiting, generalised abdominal pain & constipation. Icterus developed after average 2.6 days after admission. Mental irritation was found in 9.9%. 55% were adult males and 45% females. The mean age of patients was 25.1. The average stay in patients given plasmapheresis was 7 days without complications. INR was the guide to predict initiation of therapy. Mean Serum Bilirubin levels of 2.22 mg/dl were found. Indirect more than direct in 27.27%. Icterus presents 2.6 days after admission. Rise in bilirubin was observed after an average of 2.6 days after admission, Direct bilirubin was higher in 80%. SGOT was observed higher than SGPT in and Alkaline phosphatase was normal in 100% cases on day 1. Ammonia was observed to be in the range of 44-398 mg/dl. All patients had been subjected for psychiatric counselling and reasons for suicidal tendencies were tabulated. Alcoholism, poverty & domestic verbal violence with loved ones, were some reasons cited.

Table 2 shows details of investigations, PT INR ratios, HB & Platelet counts, Bilirubin levels with direct/indirect levels. SGOT & SGPT levels. Hepatitis ruled out as differential diagnosis. Reasons in short for suicidal consumptions. Time intervals between consumption and onset of toxicity.

	M/F	AGE	TIME TAKEN	S. BILIRUBIN	DIRECT	INDIRECT	SGOT	SGPT
CASE 1	MALE	25	6	1.6	0.7	0.9	33	28
CASE 2	MALE	26	8	2.6	1	1.6	113	78
CASE 3	MALE	32	12	1.8	0.5	1.3	45	52
CASE 4	FEMALE	30	30	7.16	2.43	4.73	381	376
CASE 5	FEMALE	23	2	1	0.5	0.5	35	28
CASE 6	MALE	25	8	2	0.8	1.2	46	68
CASE 7	MALE	30	3	3.1	1.8	1.3	23	34
CASE 8	FEMALE	25	12	2	0.8	1.2	112	96
CASE 9	FEMALE	19	36	1.6	0.7	0.9	114	34.4
CASE 10	FEMALE	19	8	2	0.9	1.1	17.6	10
case 11	male	23	48	1.6	0.5	1.1	51	32
	54.54% males	25.1818182	12.3 HRS				88.23	81.45

PT/CONTROL	PI/ INR	HBSAG/HIV	alk po4	alk po4 last	hb/plt 1	sr ammonia	ECG	XRAY CHEST
38/14	36.8% 2.71	NEG	44	56	11.3/149 x10	72	NORMAL	NORMAL
15/13.5	90% 1.11	NEG	32	54	9.8/172 x10	54	normal	normal
24/14	58.33% 1.83	NEG	67	78	16.1/160 x 10	99	NORMAL	NORMAL
23/14	68 % 2.93	NEG	46	123	12.1/99 x10	398	normal	pl effusion
14/14	1.10 91%	NEG	103	121	13.3/175 x 10	89	normal	normal
18/13.5	75%-1.33	NEG	111	116	10.1/145 x 10	56	normal	normal
23/14	60.9%-1.64	NEG	33	60	17/223 x 10	44	NORMAL	NORMAL
56/14	25% 4.29	NEG	65	84	16/190 x10	276	NORMAL	NORMAL
39/14 2.93	35% 2.93	NEG	63	68	12/226x 10	138	ISCHEMIA	NORMAL
19/14 1.36	73.7-1.36%	neg	109	145	10.3 180x10	60	normal	normal
1.33 18/13.5	75%-1.33	neg	29		17.6-187x10			
26.09 pt	72.11%	1,24 critical value of INR				128.6		

PLASMA PEHERSIS GIVEN	OUTCOME	INTENT	STAY IN
YES 5 CYCLE	3 Gms/dx5	GOOD	FIGHTS	10 days
yes 5 cycles	3gms/day/5	good	UNEMPLOYED	7 DAYS
YES 5 CYCLE	3gms/d/5	Good	ALCOHOLIC	7 DAYS
yes 5 cycles	3gms/d/5	Good	DOMESTIC VOILENCE & DOWRY ISSUE	17 days
no accidental	3gms/day/5	Good	FIGHTS	8 days
YES 5 cycles	3gms/day/5	GOOD	DEPRESSION	7 DAYS
NO SUICIDAL	3 gms/d/5	death	KNOWN MENTAL ILLNESS	1 DAY
HD , NO	3gms/d/5	DEATH	POVERTY	3 DAYS
YES 5 CYCLE	3gms/d/5	DEATH	MIGRANT POVERTY	3 DAYS
yes 5 cycles	3gms/d/5	good	LOVE AFFAIR FIGHTS.	7 DAYS
				7 days mea

pic 1 case 4 Icterus in phosphorus toxicity

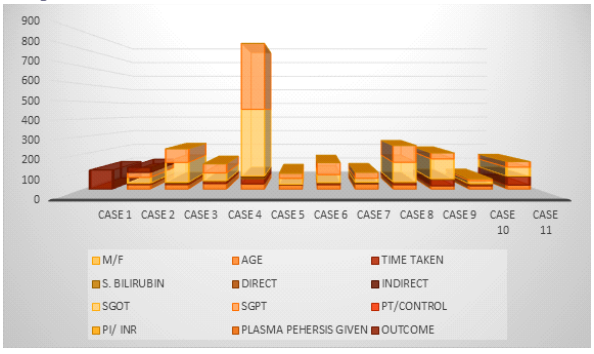
pic 2- rodenticides sold commonly over the counter. Paste & powder form.

Pic 3 showing icterus and rodenticide compounds available over the counters Plasma Filter used standard Flux P2 Dry.

Fresh Frozen plasma replacement after plasma pheresis.

Standard Protocol for plasmapheresis. Plasma Albumin 20%, Calcium gluconate, Potassium chloride. Serial clearance of plasma seen. Day 1= Haemolysed plasma, day 2 clearing from icteric to straw coloured plasma. Pic 9standard Heparin free plasmapheresis being administered therapeutically.

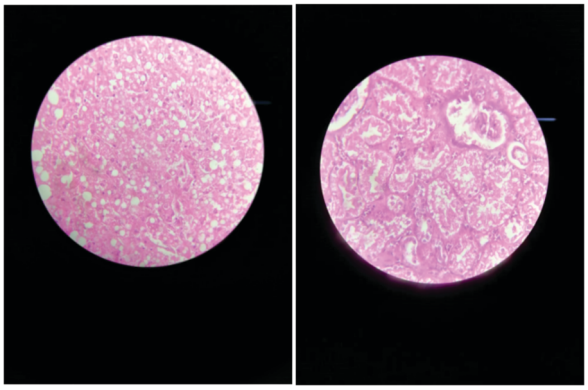
Graph 1



CONCLUSIONS & DISCUSSIONS.

Since patients responded well in first five days to plasmapheresis, an autoimmune response after consumption of Zinc phosphide or Phosphorus could be responsible for triggering the cellular damage, rather than the toxic effects of phosphorus or phosphine gas. In our study, all patients had given a history of ingestion but the physician must be aware about patients presenting with similar presentation to ask a history of accidental consumption regularly. The post mortem reports show acute fatty change and tubular necrosis in kidney and liver tissue with no detection in chemical analysis on viscera. Since the patients had consumed 3 % P containing paste, the rest 97% containing contents must be made mandatory to understand what exactly has led to the rise in fatality and quick absorption of paste to cause deaths. A ban the paste form has been recommended by S khaja et all.11In our study, Patients who were given 5 cycles of plasmapheresis along with routine supportive treatment, showed dramatic recovery to Normal state without liver cell failure or respiratory failure seen in both YP Paste & zinc phosphide poisoning cases. The possibility of platelet count and haemoglobin dropping significantly on serial analysis in only 5 days, indicate a possibility of radioactive phosphorus as a source of rodenticide preparation. No rebound platelet or haemoglobin disturbances were found after completion of plasmapheresis. Plasmapheresis worked only with INR rations between 1.17- 2.93 above which deaths were shown even with plasmapheresis. Once complications of coagulopathy had set in, the terminal events were mainly cardiac or acute renal failure. Correlating with post mortem findings, the possibility of capillary petechial bleeding in pericardium and endocardium. The liver and kidneys were main target organs affected as shown on histopathology of post mortem tissues of deceased patients. The successful innovative treatment of 5 cycles of Plasmapheresis, IV 3 Gms L Ornithine-Aspartate /day x 5 days and Im Vitamin K X 5 days given monitoring the INR ratio, was shown of benefit in this study. [$p=0.0173$, $P < 0.05$] Null hypothesis of all cases being well without Plasmapheresis was rejected. plasmapheresis benefitted the survival of 6 patients who were given plasmapheresis. It takes 3-4 days for liver toxicity to develop but coagulopathy developed in 6-24 hrs after consumption. In this study coagulation profile was seen affected much earlier than in liver cell failure with different aetiology. The contents did not contain class 1 group of anticoagulants to cause direct prolonged prothrombin time. A possibility of source of the phosphorus compound being radioactive, cannot be ruled out. Since radioactive phosphorus has been used in treatment of polycythemia and thromboasthenia. The rapid decline in HB & platelets could not be explained only by lever cell failure without significant enzyme affection or bilirubin rise. Hence a physician must capriciously suspect rodenticide consumption or accidental exposure when patients present with rapidly progressing fulminant hepatic failure with early coagulopathy and no apparent cause is found. Post mortems of deceased patients showed acute but diffused fatty changes in liver cells and early necrosis and inflammation in renal tubules on histopathology. Gross viscera could not detect yellow Phosphorus or zinc phosphide on chemical analysis. Hence only primary gastric lavage sampling during lavage obtained remains a reliable source for chemical analysis of rodenticide and should be preserved well till discharge of the patient. Post-mortem of all three patients showed similar changes on histopathology. The cerebellum showed congestion. Liver showed acute fatty changes with portal triaditis. Lungs showed septal congestion with infiltration of macrophages in interstitial. Focal fatty change was also seen in Lungs. The Heart showed interstitial congestion. Kidney showed peritubular and peri glomerular inflammation, interstitial congestion and cloudy changes. Predominant lymphocytic infiltration was seen in stomach mucosa, again indicating a T cell mediated and immune response mechanism.

Pic 9 Post Mortem Liver histopathology specimen of rodenticide poisoning showing acute fatty change, portal triaditis.



Post mortem kidney tissue histopathology specimen showing peri glomerular and peritubular inflammation.

Accidental and suicidal consumption of Rodenticides containing 3% yellow phosphorus paste and zinc phosphide are easily available as over the counter drugs in India. Suicidal consumptions in teens and adults by consuming toxic rodenticides is on the rise. Innovative Treatments for rodenticide poisonings have been advocated in the form of IV N-acetylcysteine, Vitamin K, Fresh frozen plasma, L ornithine-L-aspartate, Exchange transfusions and liver transplants. In this study, the authors have presented observations of clinical signs, symptoms, investigations, management and predictable factors for interventional plasmapheresis in the management of rodenticide poisoning. The drug rationale of using Vitamin K[Phytomenadione], LOLA- L ornithine-L aspartate and plasmapheresis has been discussed further.Vitamin K is a procoagulant administered in coagulopathy occurring due to class 1 rodenticides, namely Warfarin & Coumarin. In

YP containing compounds, the role of vitamin K comes when liver failure starts and coagulopathy occurs due to depletion of Vit K & its dependent clotting factors- Prothrombin. Adminsitration of prophylactic Vitamin K only in the Phytomenedione form, is helpful in coagulopathy. Synthetic analogues of menedione are not advocated. IM vitamin K is given as IV forms can have severe anaphylaxis reactions. The Authors hence find the use of Vitamin K justified given in the dose of 10-30 mg IM daily till PT/INR normalised . since all contents of the compound were not documented. Warfarin use has been traditionally used as rodenticide. 2]l-ornithine-l Aspartate being stable salts of 2 amino acids, their role as ammonia lowering agents has been advocated in Cochrane trials as supplementary hepatoprotective amino acids.[14] In the study, only one case showed rise in serum ammonia so administration of standard dose of LOLA in lower doses could be of hepatoprotective significance in prevention of CNS reactions occurring due to increased serum ammonia. A meta-analysis indicated association between LOLA therapy and improvement of grade I or II overt hepatic encephalopathy showed Lactulose and LOLA to be same in effectiveness to control levels of ammonia. In cases of YP oral consumption since patients were kept nil by mouth for 24 hours, IV LOLA would be a justified substitute for Lactulose given orally. [15] None of the patients showed CNS manifestations even when the serum ammonia was raised in 2 cases significantly. [Case 4,8,9.] NH^3 was significantly in deceased patients than expected in liver cell failure. Effective therapy with LOLA in liver cell failure has shown no significant advantage over lactulose [15] but when the patients are kept nil by mouth or in poisoning cases with involvement of liver where water or drugs are not advocated per orally, LOLA becomes an effective drug to be used to lower levels of serum ammonia to avoid subacute hepatic encephalopathy. Rationale of plasmapheresis in rodenticide poisoning. Exchange transfusions have been tried in 13 cases of Ratol or yellow phosphorus poisoning successfully.[17 sanchan et all.] None of the patients required ventilators, liver transplants, prolonged hospital stays for recovery, when plasmapheresis was initiated early taking PT INR as a guide to impending coagulopathy and sudden deterioration to respiratory failure or liver cell failure.

Limitations:

Small sample size for quantitative data but effective for qualitative data & factorial analysis. Required experts and technological support for treatments. Expensive therapy. Availability of plasma, platelets, albumin and blood is the precondition to therapy

Use:

Life saving measures in poisonings. The critical predictable levels for impending coagulopathy and liver cell failure may be further evaluated. The study proposes possibility of immune response, making it open for molecular & enzyme related research

ACKNOWLEDGEMENTS:

The author wishes to acknowledge departments of Forensic sciences and Pathology RGMC & CSMH for providing support to enable this study completely and thank all the free online & text references for academic access.

CONFLICT STATEMENT

The Authors have no conflict of interest or no financial interest to declare.

REFERENCES

1] Indian J Pharmacol. 2011 May-Jun; 43(3): 355–356. doi: 10.4103/0253-7613.81500 Acute hepatic failure due to yellow phosphorus ingestion Anupama Mauskar, Kunal Mehta, Leena Nagotkar, and Preeti Shanbag https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3113395/

2] 1. Brent J, Wallace KL, Burkhart KK. Phosphorus. In: Brent J, Wallace KL, Burkhart KK, Phillips SD, Donovan JW, editors. Critical Care Toxicology – Diagnosis and Management of the Critically Poisoned Patient. Philadelphia, PA: Elsevier Mosby; 2005. pp. 851–61.

3]. Fernandez OU, Canizares LL. Acute hepatotoxicity from ingestion of yellow phosphorus-containing fireworks. J Clin Gastroenterology. 1995; 21:139–42. [PubMed]

4] Shashidhara KC, Marijayanth M, Reddy PK, Kaluvakuri S. Clinical profile and outcome of rodenticide poisoning in patients admitted to a tertiary care teaching hospital in Mysore, Karnataka, India. Int J Res Med Sci 2016; 4:5023-7. https://www.msjonline.org/ index.php/ ijrms/article/viewFile/316/316

5] https://boneandspine.com/phosphorus-metabolism/ Dr Arun Pal singh

6] M. Shawkat RAZZAQUE: Phosphate toxicity: new insights into an old problem Clin Sci (Lond) Author manuscript; available in PMC 2012 Feb 1. Published in final edited form as: Clin Sci (Lond). 2011 Feb; 120(3): 91–97. doi: 10.1042/CS2010037 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3120105/

8] Razzaque MS. The FGF23-Klotho axis: endocrine regulation of phosphate homeostasis. Nat Rev Endocrinol. 2009; 5:611–61 [PubMed] http://www.vivo.colostate.edu/hbooks/pathphys/ endocrine/otherendo/vitamind.html

9] Unexpected Case of Bright Pink–Colored Plasma Kinjynarah Fifi, Marie-Aude Robert de Rancher, Charles-Emmanuel Carteret, François-Xavier Maquart, Jean-Baptiste Oudart / DOI: 10.1373/clinchem.2015.252619 Published July 2016

10] Margaret M. McCarron, Gail P. Gaddis & Alvin T. Trotter (1981) Acute Yellow Phosphorus Poisoning from Pesticide Pastes, Clinical Toxicology, 18:6, 693-711, DOI: 10.3109/15563658108990295 https://www.tandfonline.com/doi/abs/10.3109/15563658108990295

11] Indian J Crit Care Med. 2015 Feb; 19(2): 128–129. doi: 10.4103/0972-5229.151026 Should ratol paste be banned? S. Khaja Mohideen and K. Senthil Kumar

12] Indian J Crit Care Med. 2016 Jun; 20(6): 368–370. doi: 10.4103/0972-5229.183907 Successful management of zinc phosphide poisoning Vahid Shakoori,1 Mahsa Agahi,1 Maryam Vasheghani-Farahani,2 and Sayed Mahdi Marashi3

13] sciencedirect/science/article/pii/S0085253815508041 https://ac.els-cdn.com/S0085253815508041/1-s2.0-S0085253815508041-main.pdf?_tid=77e34c21-4e16-44f6-bb5d-c444da211978&acdnat=1550859239_0d0b7828e879d2ef16eb8e8640d4fe5a

14] Pol Merkur Lekarski. 2010 Jun;28(168):490-5. [Physiological functions of L-ornithine and L-aspartate in the body and the efficacy of administration of L-ornithine-L-aspartate in conditions of relative deficiency].[Article in Polish]Sikorska H1, Cianciara J, Wiercińska-Drapało A.

15] l-Ornithine-l-aspartate in the Management of Hepatic Encephalopathy: A Meta-Analysis Qian Jiang; Xue-Hua Jiang; Ming-Hua Zheng; Yong-Ping Chen DISCLOSURES J Gastroenterol Hepatol. 2009;24(1):9-14.

Books:

16] Sherlock's Diseases of the Liver and Biliary System, 13th Edition James S. Dooley (Editor), Anna S. F. Lok (Editor), Guadalupe Garcia-Tsao (Editor),Massimo Pinzani (Editor) https://www.wiley.com/en-us/search?pq=%7Crelevance%7Cauthor%3AAnna+S.+F.+Lok Public websites

Public websites

17] J Clin Apher. 2006 Jul;21(2):96-9. The effect of total plasma exchange on fulminant hepatic failure. Akdogan M1, Camci C, Gurakar A, Gilcher R, Alamian S, Wright H, Nour B, Sebastian A.T