



PREVENTION OF PHENYTOIN PRECIPITATION IN INFUSION FLUIDS

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ABSTRACT **Introduction:-** Phenytoin sodium only remains in solution when the pH is considerably alkaline (pH 10-12) but there are reports of loss of clarity when added in intravenous infusion fluids. Phenytoin precipitation is reported to occlude implanted central venous access devices and can cause irritation and tissue necrosis. Phenytoin precipitation can be prevented to avoid complications with the help of pH adjustment. **Objectives:-** To prevent phenytoin sodium precipitation in infusion fluids by pH adjustment with sodium hydroxide. **Materials And Methods :-** Physical stability of admixtures was tested in case of Phenytoin sodium in 100 ml 0.9 % w/v Normal Saline and after addition of different volumes of 5% and 10% sodium hydroxide. Physical stability was determined with visual inspection and pH measurement. **Results:-** Clear fluid was found on addition of 10% sodium hydroxide. It increases approximately 3- 4 pH when added to infusion fluid. **Conclusion:-** 1 ml of 10% Sodium hydroxide can be used to prevent phenytoin sodium precipitation in infusion fluids.

KEYWORDS : Phenytoin, Precipitation, Infusion fluids, Normal Saline

INTRODUCTION:-

Phenytoin sodium only remains in solution when the pH is considerably alkaline (pH 10-12) but there are reports of loss of clarity when added in intravenous infusion fluids (pH 4-7) [1]. Parenteral Phenytoin Sodium is indicated in management of generalized tonic clonic seizures, complex partial seizures, for prevention of seizures after head trauma and in neurosurgery [2]. Phenytoin precipitation is reported to occlude implanted central venous access device when given in glucose 5% and can be cleared by local instillation of sodium bicarbonate 8.4% to increase pH of medium. [3]

It is important to prevent the precipitation of Phenytoin Sodium often administered in infusion fluids to avoid untoward complications ranging from irritation to tissue necrosis [4]. One particular possibility could be pH adjustment of the infusion fluids. [5]

Objectives:-

1. To check whether phenytoin sodium precipitates in 0.9%w/v Normal saline.
2. To prevent phenytoin precipitation by adding Sodium hydroxide in Infusion fluids.

MATERIALS AND METHODS :-

MATERIALS :

Phenytoin sodium ampoules (50mg/2 ml) [Zydus Neurosciences, India]; 0.9% w/v Normal Saline infusion fluids (100 ml) [Denis Chem Lab, India]; 5% and 10% NaOH solution prepared in laboratory; Acid buffer 4.0, Neutral buffer 7.0 and Distilled water.

METHOD :

Preparation of Admixtures:-

1. Admixture Of Phenytoin Sodium In Infusion Fluid:-

Phenytoin Sodium was added in 100 ml Normal Saline in gradually escalating doses i.e 2,4,6,8,10,12 and 14 ml (maximum 350mg/100 ml) at room temperature. Its physical stability was evaluated at regular time intervals.

2. Addition of Sodium Hydroxide in Infusion Fluids:-

5% and 10% of Sodium Hydroxide in volumes 0.5 ml and 1 ml were added to four different 100 ml Normal Saline infusion fluids. Then, six ampoules of Phenytoin sodium i.e 300mg/2ml was added and evaluated for physical stability.

a) Admixture Physical Stability Evaluation:-

i. Visual Observation:-

Visual inspection of solutions was done after admixture preparation at regular time intervals.

ii. pH measurement:-

pH of admixture was determined using pH meter [Device was calibrated with buffers before use].

RESULTS:-

1. Admixture of Phenytoin and Normal Saline

Table 1 outlines the results of this admixture. On addition of lower doses, no changes are seen. As the dose range escalates, there is loss of clarity of Normal Saline and formation of white, insoluble, clump like precipitates [Fig.1].

Table 1 : Effect Of Mixing Phenytoin In 0.9% Normal Saline

Sr.No.	Phenytoin Sodium Volume (in ml)	Time Interval (in mins)				
		0	5	10	20	30
1	2	NP	NP	NP	NP	NP
2	4	NP	NP	NP	NP	NP
3	6	NP	NP	NP	NP	NP
4	8	NP	NP	NP	P	P
5	10	NP	NP	P	P	P
6	12	P	P	P	P	P
7	14	P	P	P	P	P



Figure 1 :- Presence Of Precipitation After Addition Of 7 Ampoules Of Phenytoin Sodium In 100 ml of NS. White Insoluble Clump Like Precipitates Are Seen.

2. Addition of Sodium Hydroxide with Normal Saline

I. Visual inspection:-

Table 2 discusses the effect of addition of NaOH to Normal Saline and Phenytoin Sodium. The clarity of infusion fluid on addition of NaOH can be well compared [Fig.2].

Table 2: Effect Of NaOH On Phenytoin In 0.9% Normal Saline

Sr. No.	Strenght of NaOH	Volume of NaOH	Observation
1	5%	0.5 ml	Precipitation Present
2	5%	1 ml	Minute precipitates seen
3	10%	0.5 ml	No precipitates
4	10%	1 ml	No precipitates



Figure 2:- Precipitation Of Phenytoin Is Visualized With Six Ampoules Of Phenytoin Sodium In 100 ml NS In Figure 2b While Clear Fluid Is Seen On Addition Of 1 ml of 10% NaOH in NS In Figure 2a.

ii. pH measurement:-
Significant difference in pH is seen on addition of NaOH.[Table 3, Figure 3] (Device had calibration of +/- 0.2)

Table 3: pH Change With NaOH On Phenytoin In 0.9% Normal Saline

Sr.No.	Strenght and volume of NaOH (%.ml)	pH obtained	pH of NS	Mean difference
1	5,0.5	8.84	6.1	2.74
2	5,1	9.08	6.1	2.98
3	10,0.5	9.65	6.1	3.55
4	10,1	10.42	6.1	4.32

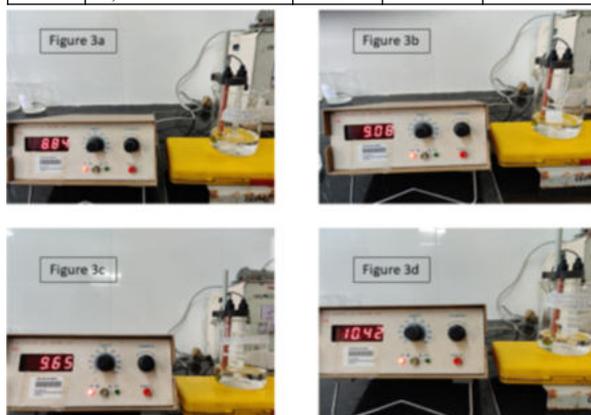


Figure 3 :- Fig 3a shows pH on Addition of 0.5ml, 5% NaOH;
Fig3b shows pH on addition of 1 ml , 5% NaOH;
Fig3c shows pH on addition of 0.5 ml,10% NaOH:
Fig 3d shows pH on addition of 1 ml, 10% NaOH

DISCUSSION:-

When two or more drugs and their diluents are mixed together in same syringe or infusion bag, there is risk of incompatibility. One such example of incompatibility is pH changes. It can cause drug to precipitate out of solution as we see in case of Phenytoin. Phenytoin is a weak acid and is formulated for intravenous use as sodium salt, with solution adjusted at highly basic pH of 12^[5].As a result when it is mixed with infusion fluid like Normal Saline with pH 4 – 7, it can tends to precipitate.

With 5% glucose(pH 3.2-6.5), it precipitates immediately and hence it should be avoided. However, it can be given in sodium chloride with pH adjustment with Sodium Hydroxide.^[6]

A study by Pfeifle et. al has shown that sodium chloride 0.9% and lactated Ringer's are suitable diluents for intravenous phenytoin sodium.^[9,10]

Previous studies done on Phenytoin precipitation has also suggested use of cyclodextrins^[7] and 8.4% sodium Bicarbonate^[3] for its prevention.

In our study, we found that 1 ml of 10% sodium hydroxide sufficiently prevents phenytoin precipitation and can be safely added to Sodium chloride infusion fluids. The main limitation was further requirement of clinical studies to support its use.

CONCLUSION:-

1 ml of 10% Sodium Hydroxide is effective alternative to prevent Phenytoin precipitation in infusion fluids.

Conflict Of Interest :-None.

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