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Pharmaceutical excipients and their potential harmful effects in neonates- a critical review

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ABSTRACT :

Pharmaceutical recipients used in pediatric formulations have received significant attention from regulatory agencies worldwide due to the safety concerns. Many excipients have been implicated in interfering with the growth and development process of pediatric population. Our aim was to describe the extent of excipients intake in neonates, to classify the excipients according to potential neonatal toxicity to ensure safety and efficacy of such products.

KEY-WORDS: Potential neonatal toxicity, Harmful excipients, Patient safety and Acceptability, Pediatrics

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INTRODUCTION:

Different dosage forms formulated now a day's contain both pharmacologically active and inactive ingredients. The therapeutically inactive ingredients of a medicine are considered as Excipients. The Excipients perform many critical functions like: acting as diluent, wetting agents, binders, solvents, absorption enhancers, fillers, preservatives, sweeteners, coloring, flavoring and stabilizing agents etc. These Excipients converts medicinal compound to an improved elegant pharmaceutical product for clinical use. According to regulatory requirements, excipients have to be appropriately evaluated for safety similar to active pharmaceutical ingredients, in most instances the safety data of excipients is based on adult exposure. Thus, information about their acceptability and safety in relation to the age and development status of child is lacking. Neonates are the most vulnerable patient population when adverse effects of excipients are considered. This is mainly due to organ immaturity and difference in pharmacokinetics and pharmacodynamic profiles when compared to adults [1, 2, 3, 4].

EXCIPIENT:

The word excipient is derived from the Latin word Excipere, meaning 'to except',it is simply explained as 'other than'. "Pharmaceutical Excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

ROLE OF EXCIPIENTS

Excipients have different roles in a formulation such as

- Aid in the processing of the drug delivery system during its manufacture
- Assist in product identification and enhance any attribute of the overall safety
- Protect, support or enhance stability, bioavailability and patient acceptability
- Assist in maintaining the integrity of the drug product during storage
- Assist in the effectiveness or delivery of the drug in use.

Table:1 Most Common Adverse Effects Encountered With Excipients Included In Pediatric Population:

EXCIPIENTS	EXAMPLE	ALLOWABLE DAILY INTAKE (ADI)	ADVERSE EFFECTS
Diluents	Micro crystalline cellulose	Not specified	Intestinal absorption, long term effect not known , should not use children < 2yrs
Solvents and co-solvents	Benzyl alcohol	Not specified	Severe respiratory complications and even death in neonates caused by dilution of nebulization solutions with benzyl alcohol preserved saline. Toxic syndrome observed in neonates due to the practice of "flushing out" umbilical catheters with solutions containing benzyl alcohol.
	Ethyl alcohol	Max 10% (12yrs) Max 5% (6-12yrs) Max 0.5%(<6yrs)	CNS effects at 0.01g/l; intoxication, lethargy, stupor, coma, respiratory depression, cardiovascular collapse due to high blood brain barrier permeability.
	Peanut oil	Not specified	Leads to episodes of hypersensitivity
	Propylene glycol	25mg/kg	Toxic dose not known, but potential life threatening complications such as cardiovascular, hepatic, respiratory and CNS adverse reactions especially in neonates where the biological half- life is prolonged to 17 hrs compare with adult 5hrs.
	Hydroxypropyl beta cyclodextrin		Nephrotoxicity
Dyes	"E number " additives: Sunset yellow (E110), Quinoline yellow (E104), Camoisine (E122), Allura red (E129), Tartarazine (E102), Ponceau4R (E124)	2.5 mg/kg (sunset yellow)	Negative effect on children's behavior and ADHD
Surfactants	Polysorbate 80	10mg/kg/ day	E- Ferol syndrome Thrombocytopenia, renal dysfunction, hepatomegaly, chlestasis, ascites, hypotension and metabolic acidosis can be seen in low birth weight infants.
	polyvinylpyrrolidone	0 – 50 mg/kg	Not specified
Preservatives	Benzoic acid Potassium benzoate Sodium benzoate	Upto 5mg/kg (sum of all)	Caffeine and benzoate should be injected simultaneously; elicits non-immunological contact reactions including urticaria& atopic dermatitis in neonates.
	Thimerosal	Not specified	Possible link with toxicity in pediatric vaccines and childhood autism; though unproven.

Sweeteners	Aspartame	40mg/kg/day	Source of phenylalanine, can cause phenylketouria; hyper activity in children but un proven
	Lactose	Not specified	Diarrhoea, gaseousness or cramping and intestinal disorders.
	Saccharin	5mg/kg/day	Pediatrics with allergy to sulphonamides should avoid saccharin; carcinogenic potential (banned in Canada).
	Sorbitol	0.3mg/kg/day	Diarrhea, GIT disorders.
	sucralose	5mg/kg/day	Not specified
Plasticizers	Di-butyl phthalates Di-ethylphthalates	<0.1mg/kg/day	Disrupt endocrine synthesis, secretion, transport, binding action, elimination of natural hormones in the body.
	Diethylhexylphathalates	0.02 mg/kg/day	Reproduction deformities, developmental abnormalities of fetus.

LITERATURE DATA:

From the analysis of the literature, limited to a relatively few number of articles (Tab-2). Emerges that almost all drugs used in neonates (including licensed) containat least one potential harmful excipient is and the safety of the majority of these excipients is not easily assessable based on information contained in the SPCs(State Plane Coordinate System).

A European observational study described the extent of the administration of eight potentially harmful excipients (benzoates, Parabens, saccharin sodium, sorbitol, benzalkonium, ethanol, polysorbate80 propylene glycol) in 89 third-level NICUs from 21 countries. Among 2,095 prescriptions (530 different products) administered to 726 neonates (477 preterm), the presence of potentially harmful excipients was found in 31% of prescriptions (142 products) and involved 456 neonates (63%). Parabens were used most frequently, followed by propylene glycol and benzoates. Major determinants resulted geographical area, gestational age and route of administration. In detail, variation of excipient administration reflected prescription behavior among countries (for ex- the different proportion of vitamin prescriptions containing parabens or the non use of domperidone containing saccharin sodium in the East Europe); term neonates were less likely to receive Parabens, benzoates and ethanol; enteral and topical formulations contained more frequently potentially harmful excipients. A few commonly used medicines were responsible for a large part of potentially harmful excipients, therefore a substitution or a reformulation of products may spare many neonates from unnecessary exposure.

Table-2: Summary Of Studies Reporting Exposure To Potentially Harmful Excipients In Nicus.

Reference	Country/area	Study period	Number of neonates	Number of prescriptions	Number of products	Number of products containing PHE(%)	Number of PHE (%)	Number of exposed neonates
Nelis, 2015(6)	Europe	1day	726	2,095	530	142 (27%)	n.i.	456 (63%)
Garcia-palop,2016(7)	Spain	n.i.	n.i.	n.i.	101	40 (40%)	n.i.	n.i.
Souza, 2014(8)	Brazil	3 months	79	1,303	77	48 (62%)	57 (66%)	78 (99%)
Lass,2012(8)	Estonia	1 yr	348	1,961	107	73 (68%)	47 (38%)	339 (97%)
Whittaker,2009 (9)	UK	1 yr	38	n.i.	n.i.	n.i.	7 (35%)	n.i.
Shehab,2009(10)	USA	1 yr	1,190	170	n.i.	15	2	459 (39%)
Fister, 2015(11)	Slovenia	1 month	48	n.i.	27	18 (66%)	29 (48%)	48 (100%)
Butler, 2007(12)	UK	4 weeks	14	n.i.	29	16 (56%)	4	14 (100%)

PHE: potentially harmful excipients, n.i.: not indicated, NICUs: Neonatal Intensive Care Units.

There are different formulations, but the synthetic Vitamin K shot has similar toxic ingredients as vaccines, including benzyl alcohol, polysorbate 80 and aluminum. All of these ingredients are linked to short and long-term health issues.

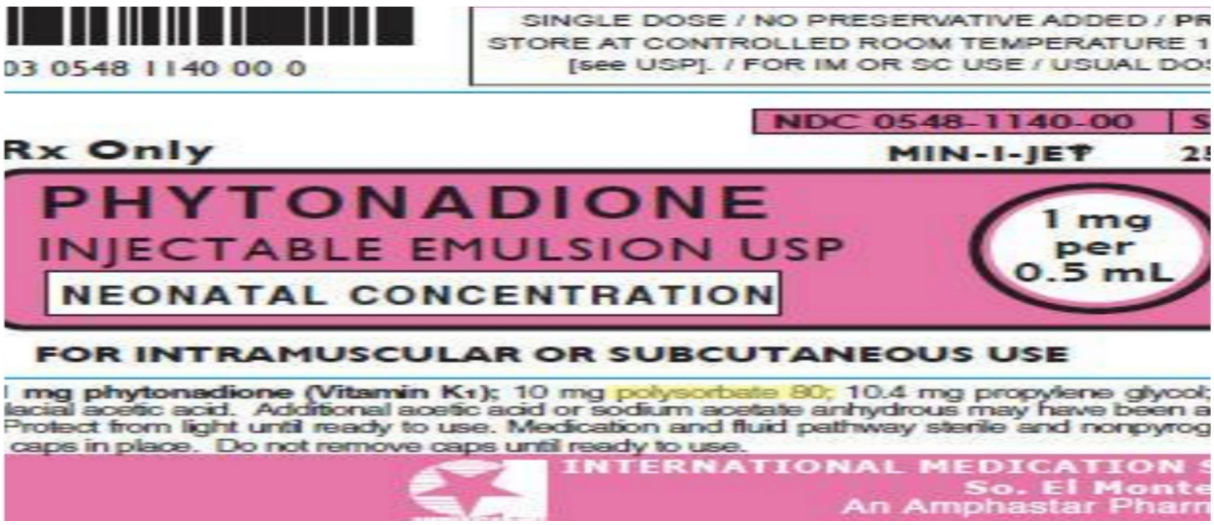

Figure 1 : Vitamin K has toxic ingredients as vaccines.

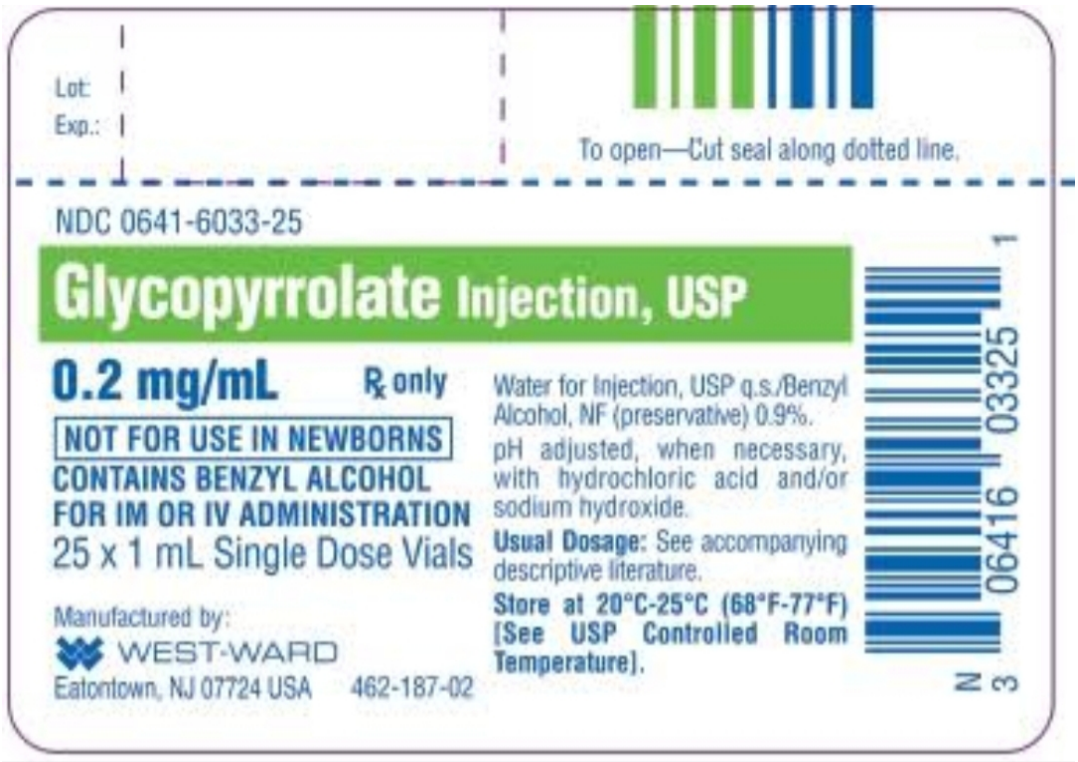

Figure 2 : Benzyl alcohol containing drug that should not be used for neonates

Fig-3 Example for Alcohol containing cough syrup

REGULATORY GUIDELINES AND PEDIATRIC FORMULATIONS:

Development of formulations for pediatrics is challenging since regulatory guidelines that govern the development of dosage forms for pediatric consumption have not been fully implemented worldwide. The international pharmaceutical excipients council (IPEC), the European medicines agency (EMA), and Centre for drug evaluation research (CDER) of the US Food and Drugs Administration (FDA) have provided guidelines for conducting preclinical studies for the safety evaluation of pharmaceutical excipients in 1997, 2003, 2005, 2013 respectively.[4,13] These guidelines provide frame work for short term and long term safety testing of excipients for adult dose consumption. Though there are provisions for reproductive testing of excipients, none of the guidelines recommended conduct the ADME studies over the entire pediatric age group for which the drugs and excipients will be used.

Formulations developed for pediatric use need to meet certain criteria including development of appropriate route of administration that would complaint with pediatric age group; orally dissolving; tasteless; show adequate light, humidity, and heat stability; amenable to dose titrations such that they can be dispensed to pediatric population from pre-term new-born infants (<37 weeks

of gestation) to adolescents (12-18 yrs). Have suitable drug release patterns [3, 4]. Excipients used in developing such formulations for pediatric consumption therefore must meet certain safety criteria.

CONCLUSION

Neonates are commonly receiving a wide range of excipients with their medications. Preservatives and artificial sweeteners used as excipients may cause harm to the exposed neonatal and pediatric patients. This study aimed to assess the true impact of excipients toxicity. Quantitative information about excipients should be made available to pharmacists and neonatologists helping them to take into account excipient issues when selecting medicines and to monitor for adverse effects if administration of medicines containing excipients is unavoidable.

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