SMOFlipid formulation

Newborn use only

2023

<table>
<tr><td>Alert</td><td>SMOFlipid should always be a part of a complete parenteral nutritional treatment including amino acids and glucose.</td></tr>
<tr><td>Indication</td><td>As part of parenteral nutrition</td></tr>
<tr><td>Action</td><td>SMOFlipid compounded formulation provides essential fatty acids, non-carbohydrate energy, fat and water-soluble vitamins. SMOFlipid contains soybean oil (30%), medium chain triglyceride (30%), olive oil (25%) and Fish oil (15%).</td></tr>
<tr><td>Drug type</td><td>Lipid emulsion.</td></tr>
<tr><td>Trade name</td><td>SMOFlipid compounded formulation – supplied by Fresenius-Kabi.</td></tr>
<tr><td>Presentation</td><td>SMOFlipid compounded formulation prepared by Fresenius-Kabi:
1. 45 mL syringe FKS 045V
2. 50 mL syringe FKS050V
2. 151 mL bag FKC PLV1.

<table>
<tr><th>Contents</th><th>45 mL syringe
For ≤1 Kg</th><th>50 mL syringe
For ≤1 Kg</th><th>151 mL bag
For >1 Kg</th></tr>
<tr><td>SMOFlipid 20%</td><td>32.5 mL</td><td>36 mL</td><td>109 mL</td></tr>
<tr><td>Soluvit N</td><td>2.5 mL</td><td>2.8 mL</td><td>8.4 mL</td></tr>
<tr><td>Vitalipid N Infant</td><td>10 mL</td><td>11.2 mL</td><td>33.5 mL</td></tr>
<tr><td>FK code</td><td>FKS045V</td><td>FKS050V</td><td>FKCPLV1</td></tr>
<tr><td>Stability</td><td>13 days at 2^0-8^0C</td><td>13 days at 2^0-8^0C</td><td>12 days at 2^0-8^0C</td></tr>
</table>

There are other strengths of compounded formulations available. Please check with your local facility.</td></tr>
<tr><td>Dose</td><td>1-3 g/kg/day
Equates to the volumes of the compounded formulation that contains 80% of water*
<table>
<tr><th>Lipid, g/kg/day</th><th>SMOFlipid volume, mL/kg/day</th><th>Water content</th></tr>
<tr><td>1 g/kg/day</td><td>6 mL/kg/day</td><td>5 mL/kg/day</td></tr>
<tr><td>2 g/kg/day</td><td>12 mL/kg/day</td><td>10 mL/kg/day</td></tr>
<tr><td>3 g/kg/day</td><td>18 mL/kg/day</td><td>15 mL/kg/day</td></tr>
</table>
*Due to the significant water content, SMOFlipid can be counted in the total volume of fluid intake.</td></tr>
<tr><td>Dose adjustment</td><td>consider reducing the dosage of lipid emulsions, if triglyceride levels >3.0 mmol/L, [1] but consider continuing at least 0.5g/kg/day to prevent essential fatty acid deficiency.</td></tr>
<tr><td>Maximum dose</td><td>3 g/kg/day</td></tr>
<tr><td>Route</td><td>IV</td></tr>
<tr><td>Preparation</td><td>No preparation is required for compounded formulation. Syringes and bags are supplied in light protected packaging.</td></tr>
<tr><td>Administration</td><td>Continuous IV infusion over 24 hours.
Protect from light.
DAILY volume may also be administered over 20 hours.
Maximum hang time at room temperature is 48 hours.</td></tr>
<tr><td>Monitoring</td><td>IV site for extravasation.
Serum triglycerides - once at 24 hours after the completion of 1,2 and 3g/kg/day and then, weekly or if baby is ill until the infusion is ceased.
blood glucose, electrolytes, liver and renal function, full blood count as routine laboratory monitoring during complete parenteral nutrition.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to fish-, egg-, soya- or peanut protein or to any of the active substances or excipients.
Severe hyperlipidaemia.
Severe liver insufficiency.
Severe blood coagulation disorders.
Severe renal insufficiency without access to hemofiltration or dialysis.
Acute shock.
General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, decompensated cardiac insufficiency.</td></tr>
<tr><td>Precautions</td><td>Hepatic impairment
Impaired lipid metabolism which can occur in sepsis, renal or hepatic impairment.
Unstable conditions (e.g. severe metabolic acidosis, severe sepsis and hypotonic dehydration).</td></tr>
</table>

Drug interactions

The addition of medications other than water- and fat-soluble vitamins as compounded in these formulation should be avoided.

Adverse reactions

Hypertriglyceridemia.
Fat overload syndrome – Not reported in neonates. In adults, it is characterised by hyperlipemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leukopenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued.

Compatibility

These recommendations are extrapolated from 4 studies[3-5,11] and the SMOFlipid formulations used in those studies may differ from our formulations. If there is any existing incompatibility between a medication and a pure soybean-based ILE, then it would remain incompatible with Smoflipid.[3] However, one cannot assume that compatibility with intralipid equates compatibility with SMOFlipid as SMOFlipid contains mixed lipids, not pure soybean oil.

Fluids: Mixing SMOFlipid compounded formulation with other solutions should be avoided. Sodium chloride 0.9%, amino acid-glucose solution.

Y-site:

Drug	Drug concentration	Y-site compatibility
Amoxicillin	100 mg/mL	Yes
Ampicillin	30 mg/mL; 100 mg/mL	Yes
Benzylpenicillin	100 mg/mL	Yes
Caffeine (base)	10 mg/mL	Yes
Dexmedetomidine	4 mcg/mL	Yes
Fentanyl	50 mcg/mL	Yes
Furosemide	10 mg/mL	Yes
Heparin	500 units/mL	Yes
Hydromorphone	2.5 mg/mL	Yes
Ibuprofen	1.25 mg/mL; 5 mg/mL	Yes
Ibuprofen lysine	4 mg/mL	Yes
Indometacin	200 mcg/mL	Yes
Ketamine	10 mg/mL	Yes
Midazolam	0.5 mg/mL	Yes
Milrinone	200 mcg/mL	Yes
Morphine hydrochloride	500 mcg/mL	Yes
Morphine sulfate	500 mcg/mL; 1 mg/mL	Yes
Paracetamol	10 mg/mL	Yes
Sildenafil	0.8 mg/mL	Yes

Y site - Other[7]
Aminophylline, ampicillin, aztreonam, calcium gluconate, cefazolin, cefoperazone, cefotaxime, cefoxitin, ceftazidime, clindamycin, cloxacillin, dexamethasone sodium phosphate, digoxin, dobutamine, enalaprit, erythromycin lactobionate, fentanyl citrate, fluconazole, hydrocortisone sodium phosphate, insulin, regular, isoproterenol, lidocaine, magnesium sulfate, meropenem, methylprednisolone sodium succinate, metronidazole, miconazole, nitroglycerin, norepinephrine bitartrate, octreotide acetate, penicillin G potassium (not sodium), pentoxifylline, piperacillin-tazobactam, potassium chloride, sodium bicarbonate, sodium nitroprusside, tacrolimus, ticarcillin disodium, trimethoprim-sulfamethoxazole, vancomycin HCL, zidovudine.

Incompatibility

Fluids: Mixing SMOFlipid compounded formulation with other solutions should be avoided.
Y-site:[7] Aciclovir, Alprostadil, amikacin sulfate, amphotericin B, ceftriaxone, dopamine, doxycycline, famotidine, ganciclovir, gentamicin, lorazepam, midazolam, phenobarbital, rocuronium.

Drug	Drug concentration	Y-site compatibility
Alprostadil	20 mcg/mL	No
Caffeine citrate	20 mg/mL	No
Dopamine	3.2 mg/mL	No
Famotidine	2.5 mg/mL	No
Gentamicin	2 mg/mL; 10 mg/mL	No

	Rocuronium	10 mg/mL	No
Stability	45 mL syringe: 13 days at 2-8^{0}C; 151 mL syringe: 12 days at 2-8^{0}C		
Storage	Compounded formulations are to be stored in refrigerator once they arrive the NICU.		
Excipients	Glycerol, Egg Lecithin, dl-alpha-Tocopherol, Sodium Hydroxide, Sodium Oleate, Water for injections		
Special comments	Due to the significant water content, SMOFlipid can be counted in the total volume of fluid intake.		

Evidence

Background

Intravenous lipid emulsions (ILEs) are an indispensable part of paediatric parenteral nutrition (PN). ILE provides a noncarbohydrate source of energy delivered as an iso-osmolar solution in a low volume (2.0 kcal/mL with 20% ILEs, or 1.1 kcal/mL with 10% ILEs). Generally, a lipid intake of 25-50% of non-protein calories is recommended in fully parenterally fed infants. Lipids provide essential fatty acids (EFAs) and help with the delivery of the water- and fat-soluble vitamins.

Efficacy

Recent meta-analyses and RCTs provide evidence that the initiation of lipids within the first two days of life in very preterm infants appears to be safe and well tolerated. No signs of increased respiratory impairment, chronic lung disease, sepsis, patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhages, retinopathy of prematurity, or mortality could be demonstrated. Observational studies also suggested that early initiation of ILE influences later neurodevelopment. To date there is no evidence that gradual increments in the infusion rate of lipids improve fat tolerance.

ESPGHAN 2018 recommendations:

1. In preterm infants, lipid emulsions can be started immediately after birth and no later than on day two of life and for those in whom enteral feeding has been withdrawn, they can be started at time of PN initiation.
2. In preterm and term infants, parenteral lipid intake should not exceed 4 g/kg/day.
3. In children, parenteral lipid intake should be limited to a maximum of 3 g/kg/day.
4. In order to prevent essential fatty acids (EFA) deficiency in preterm infants a lipid emulsion dosage providing a minimum linoleic acid (LA) intake of 0.25 g/kg/day can be given. This equates to 1 g/kg/day of SMOFlipid as a minimum.
5. In order to prevent EFA deficiency in term infants and in children a lipid emulsion dosage providing a minimum LA intake of 0.1 g/kg/day can be given. This equates to 0.5 g/kg/day of SMOFlipid as a minimum.
6. Pure soybean oil (SO) ILEs (e.g. Intralipid) may provide less balanced nutrition than composite ILEs (e.g. SMOFlipid).
7. For PN lasting longer than a few days, pure SO ILEs should no longer be used and composite ILEs with or without fish oil (FO) should be the first choice treatment. SMOFlipid is a composite ILE wit fish oil.
8. In preterm infants, ILEs should be protected by validated light-protected tubing.
9. 20% ILEs (e.g. SMOFlipid 20%) should be the first choice treatment.
10. In newborns including preterm infants, routine use of ILEs should be continuous over 24 hours. If cyclic PN is used, for example for home PN children, ILEs should usually be given over the same duration as the other PN components.
11. In paediatric patients, heparin should not be given with lipid infusion on a routine basis. (LoE 3e4, GPP, conditional recommendation for)
12. In paediatric patients with sepsis, more frequent monitoring of plasma triglyceride concentration and dose adjustment in case of hyperlipidaemia are recommended. ILE dosage may be reduced but lipid supply may generally be continued at least in amounts supplying the minimal EFA requirements.
13. In patients with severe unexplained thrombocytopaenia, serum triglyceride concentrations should be monitored and a reduction of parenteral lipid dosage may be considered.
14. As part of measures to reverse IFALD in paediatric patients, a discontinuation of SO ILE, (e.g. Intralipid), a reduction of other ILE dosage and/or the use of composite ILE with FO (e.g. SMOFlipid), should be considered along with the treatment and management of other risk factors.
15. The use of pure Fish oil ILE (e.g. omegaven) is not recommended for general use in paediatric patients but may be used for short-term rescue treatment in patients with progression to severe Intestinal failure associated liver disease, based on case reports.

16. Markers of liver integrity and function, and triglyceride concentrations in serum or plasma should be monitored regularly in patients receiving ILEs, and more frequently in cases with a marked risk for hyperlipidaemia (e.g. patients with high lipid or glucose dosage, sepsis, catabolism, extremely low birth weight infants).
17. Reduction of the dosage of ILEs can be considered if serum or plasma triglyceride concentrations during infusion exceed 3 mmol/L (265 mg/dL) in infants.

Safety

A systematic review suggested that the ILEs initiated within the first 2 d of life in VLBW infants appears to be safe and well tolerated.[8] In this meta-analysis, type of lipid also did not show any significant difference in growth during hospital admission, death, bronchopulmonary dysplasia, duration of respiratory support and supplemental oxygen, necrotising enterocolitis, hypertriglyceridemia, and hyperglycemia.[8] ILEs do not seem to affect platelet number or platelet function.[1] However, some concerns were raised regarding the effect of ILEs on platelet aggregation. ESPGHAN 2018 recommendation: In patients with severe unexplained thrombocytopenia, serum triglycerides should be monitored and a reduction in lipid dosage may be considered.[1]

Fat overload syndrome: Characterized by fever, jaundice, hepatosplenomegaly, respiratory distress, and spontaneous haemorrhage. Other symptoms include anaemia, leukopenia, thrombocytopenia, low fibrinogen levels and coagulopathy. Although this was most often reported with rapid infusion of pure Soy oil ILEs, it was also reported with accidental, rapid infusion of SMOFlipid in a 2-year old girl, suggesting the rate of infusion is responsible. The patient was successfully treated with supportive care combining fluid infusion, transfusion of platelets, and substitution of serum albumin (0.5 g/kg/d) and fresh-frozen plasma (10 mL/kg). In the next couple of days, she received extra platelets, erythrocyte transfusion, and filgrastim (Neupogen; 5 µg/kg/d) due to a very low leukocyte count.[9]

Hypertriglyceridemia: Hypertriglyceridemia (HT) is common in extreme preterm infants. A retrospective review of 195 infants <29 weeks gestation showed HT in 33% in 23-25 weks and 16% in 26-28 weeks. Severe HT (Plasma triglyceride >4.5mmol/L) was noted in 10% in 23-25 weeks and 4.5% in 26-28 weeks gestation. In this study, there were no overt signs of fat overload directly attributable to LE, however, 2 infants developed transient mild thrombocytopenia and 1 infant developed transient pancytopenia, coinciding with the severe HT. There were no episodes of liver dysfunction or cholestasis associated with severe HT. The number of infants who developed HT at 1 g/kg/day, 2 g/kg/day and 3 g/kg/day were 1.5%, 3.6% and 14.4% respectively.[10]

Practice points

Estimated vitamin intakes in **preterm** neonates with 3 g/kg/day of SMOFlipid formulation

Unit/kg/day	ESPGHAN 2018 Day 0	ESPGHAN 2018 Growing	3 g/kg/day of lipid formulation
Vit A, IU	700-1500	700-1500	920
Vit D, IU	80-400	80-400	160
Vit E, IU	2.8-3.5	2.8-3.5	2.8
Vit K, µg	10	10	80#
Thiamine, µg	350-500	350-500	310
Riboflavin, µg	150-200	150-200	360#
Niacin, mg	4.0-6.8	4.0-6.8	4
Pyridoxine, µg	150-200	150-200	400#
Folate, µg	56	56	40*
Vit B12, µg	0.3	0.3	0.5#
Pantothenate, mg	2.5	2.5	1.5*
Biotin, µg	5-8	5-8	6
Vit C, mg	15-25	15-25	10*

Estimated vitamin intakes in **term** neonates with 3 g/kg/day of SMOFlipid formulation

Nutrient, Unit/kg/day	**ESPGHAN 2018**	**3 g/kg/day of lipid formulation**
Vit A, IU	462-989	920
Vit D, IU	40-150	160
Vit E, IU	2.8-3.5	2.8
Vit K, µg	10	80#

	Thiamine, µg	350-500	310
	Riboflavin, µg	150-200	360#
	Niacin, mg	4.0-6.8	4
	Pyridoxine, µg	150-200	400#
	Folate, µg	56	40*
	Vit B12, µg	0.3	0.5#
	Pantothenate, mg	2.5	1.5*
	Biotin, µg	5-8	6
	Vit C, mg	15-25	10*

References

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Parker B, Callander I, Allegaert K. SMOFlipid formulation. Consensus formulary by the Australasian Neonatal Medicines Formulary group. Version 1, dated 30 November 2023. www.anmfonline.org