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Professeur Farshid Sadeghipour
Professeur Pascal Bonnabry

Utilisation rationnelle des émulsions parentérales dans un Service de soins intensifs adulte

THÈSE

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par

Jean-Christophe Devaud

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La Faculté des sciences, sur le préavis de Monsieur F. SADEGHIPOUR, professeur titulaire et directeur de thèse (Pharmacie du Centre hospitalier universitaire vaudois, Lausanne, Suisse), Monsieur P. BONNABRY, professeur associé et codirecteur de thèse (Section des sciences pharmaceutiques), Monsieur J.-L. WOLFENDER, professeur ordinaire (Section des sciences pharmaceutiques), Monsieur S. LIMAT, professeur (Centre hospitalier régional universitaire, Hôpital Jean Minjoz, Besançon, France), Monsieur A. PANNATIER, professeur (Vice-président de la Commission cantonale d'éthique de la recherche sur l'être humain, Lausanne, Suisse) et P. VOIROL, docteur (Pharmacie du Centre hospitalier universitaire vaudois, Lausanne, Suisse), autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

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Résumé du travail de thèse

Les émulsions lipidiques sont couramment utilisées en soins intensifs comme apport nutritionnel et non nutritionnel. L'utilisation de cette forme galénique peut entraîner des perturbations du profil lipidique des patients de soins intensifs mais peut également être à l'origine d'infections acquises en milieu hospitalier.

Le but de ce travail a été de mettre en place une utilisation rationnelle de ces émulsions dans une unité de soins intensifs visant à diminuer les perturbations du profil lipidique et les infections associées.

Le **chapitre I** introduit la problématique de l'utilisation des émulsions lipidiques dans les unités de soins intensifs. Il dresse un aperçu des effets secondaires et des coûts potentiels associés à l'utilisation d'une telle forme galénique.

Le **chapitre II** présente la première étude de ce travail et étudie l'influence que peut avoir un type de lipides donné dans une émulsion et l'impact que ce dernier peu avoir sur la triglyceridémie des patients de soins intensifs.

Le **chapitre III** présente un effet secondaire inattendu d'un sédatif largement utilisé aux soins intensifs : Le propofol. La molécule de propofol semble avoir un effet sur le métabolisme des émulsions lipidiques chez les patients de soins intensifs contribuant ainsi à perturber encore plus leur profil lipidique.

Le **chapitre IV** compare deux conditionnements différents du propofol, un anesthésique formulé dans une émulsion lipidique, dont l'un est prêt à l'emploi et l'autre est à conditionner avant administration. Ce travail analyse la prévalence des infections et les coûts associés chez les patients de soins intensifs lors d'une telle administration parentérale.

Le **chapitre V** conclut ce travail de thèse en confirmant l'intérêt qu'offre un suivi de l'utilisation des émulsions lipidiques dans une unité de soins intensifs en vue d'assurer la sécurité des patients ainsi qu'un contrôle des coûts potentiels associés à leur utilisation.

Communications scientifiques

Les résultats de ce travail de thèse ont fait l'objet de publication dans des revues internationales ou ont été présentés lors de congrès suisses ou internationaux en tant que présentation affichées :

Publications

Devaud J.-C., Berger MM, Pannatier A, Marques-Vidal P, Tappy L, Rodondi N, Chiolero R, Voirol P. Hypertriglyceridemia: a potential side effect of propofol sedation in critical illness. Intensive Care Med. 2012 Dec;38(12):1990-8.

Devaud J.-C., Eggimann P., Voirol P., Jolliet P. Pinget C., Wasserfallen J.-B., Pannatier A. Costs evaluations of ready-to-use propofol syringes versus syringes drawn from vials in critically ill. Value in Health, 16(7), A323-A636, 2013

Devaud J.-C, Voirol P, Marques-Vidal P, Tappy L, Rodondi N, Berger M.M, Chioléro R, Pannatier A. Risk factors for hypertriglyceridemia in the intensive care unit (ICU) : an exploratory study. Critical Care, 14, (Suppl 1), 586, 2010

Les publications suivantes concernent l'utilisation des medicaments en milieu hospitalier mais le sujet n'est pas traité dans ce travail de thèse :

Devaud J.-C., Sigrist T., Zaugg C., Guignard B., Pannatier A., Bonnabry P. Proposition d'une marche à suivre pour la gestion et la prévention d'extravasation d'agents non cytotoxiques. Pharmactuel, 45(2), 132-136, 2012

Présentations affichées (posters)

Devaud J.-C, Berger MM, Voirol P, Pannatier A, Sadeghipour F. Does the type of your parenteral lipids matter ? a clinical answer in ciritical illness. 19èmes Journées Franco-Suisses de Pharmacie Hospitalière. Macon 23-24 avril 2015.

Devaud J.-C., Eggimann P.P., Voirol P., Jolliet P., Pinget C., Wasserfallen J.-B., Pannatier A., Sadeghipour F. Ready-to-use propofol syringes: pharmacoeconomic modelisation of their potential to reduce primary bacteraemia in critically ill patients. 2ème congrès suisse des pharmaciens (GSASA-PharmaSuisse), Interlaken, 2-4 novembre 2014.

Devaud J.-C., Eggimann P., Voirol P., Jolliet P., Pinget C., Wasserfallen J.-B., Pannatier A. Costs evaluations of ready-to-use propofol syringes versus syringes drawn from vials in critically ill ISPOR 16th Annual European Congress, Dublin, 2-6 novembre 2013

Devaud J.-C, Voirol P, Marques-Vidal P, Rodondi N, Berger MM, Chiolero R, Tappy L, Pannatier A. Risk factors for hypertriglyceridemia in intensive care unit (ICU) an expolratory study. 16èmes JFSPH, Sion, 18-19 novembre 2010 et poster 30th International Symposium on Intensive Care and emergency medicine, Bruxelles, 9-12 mars 2010.

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Plüss-Suard C. Devaud J.-C., Sadeghipour F. Zanetti G. Senn L. Prospective surveillance of daptomycin and intravenous colistin use after implementation of new guidelines. 19èmes Journées Franco-Suisses de Pharmacie Hospitalière. Macon 23-24 avril 2015.

Devaud JC, Voirol P, Cavassini M, Pannatier A. Impact of a preformatted outpatient prescription form for anti-HIV drugs. 34th European Symposium on Clinical Pharmacy, Amsterdam, 26-29 octobre 2005 et Congrès annuel de la GSASA, Zurich, 24-25 novembre 2005.

Pavie P, Grouzmann M.C, Lamon S, Devaud J-C, Berger M, Chianese R, Podilsky G, Pannatier A. Application d'une matrice occurence-conséquences dans l'analyse de risque d'un processus de fabrication hospitalière 17èmes JFSPH, Lons-le-Saunier, 15-16 Mars 2012.

Bouchoud L., El-Hadeuf W., Adamo V., Schwebel H., Devaud J.-C., Pannatier A., Bonnabry P. Mise au point d'une forme sèche de nutrition parentérale pédiatrique à destination des pays en développement (communication orale), 10èmes JFN, Lyon, 12-14 décembre 2012.

Pavie P., Podilsky G., Devaud J.-C., Pannatier A. Training and Qualification of Manufacturing Operators in French and Swiss Hospitals: A Survey (communication orale) 15èmes journées du GERPAC / 10èmes journées européennes du GERPAC, Presqu'île du Ponant, La Grande Motte, 3-5 octobre 2012.

Abréviations

ALAT Alanine aminotransférase

ALISIA Alimentation soins intensifs adulte

Apo Apolipoprotéine

ARN Acide ribonucléique

BMI Body mass index ou indice de masse corporelle

CHUV Centre hospitalier universitaire vaudois

DCI Dénomination commune internationale

HDL High density lipoprotein ou lipoprotéine de haute densité

HTG Hypertriglyceridémie

IDL Intermediate density lipoprotein ou lipoprotéine de densité intermédiaire

IL Interleukine

LCT Long chain triglycerides ou triglycérides à chaîne longue

LDL Low density lipoprotein ou lipoprotein de faible densité

LPL Lipoprotéine lipase

MCT Medium chain triglycerides ou triglycérides à chaîne moyenne

PMJ Posologie maximale journalière

SCT Short chain triglycerides ou triglycérides à chaîne courte

SI Soins intensifs

SMIA Service de médecine intensive adulte

STG Structured triglycerides ou triglycérides structurés

TG	Triglycéridémie
TNF	Tumor necrosis factor ou facteur de nécrose tumorale
VLCT	Very long chain triglycerides ou triglycérides à chaîne très longue
VLDL	Very low density lipoprotein ou lipoprotéine de très faible densité
Γ- GT	Γ-Glutamyltranspeptidase

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CHAPITRE I

Introduction générale

1. Introduction

La science de la nutrition a longtemps balancé entre la science et la technologie. De grands noms de la chimie se sont illustrés dans les deux activités, toutes deux essentielles quand les patients hospitalisés souffraient périodiquement de dénutrition.

Nous ne reviendrons pas ici sur la différence entre science et technologie : la première cherche les mécanismes des phénomènes, tandis que la seconde utilise les résultats de la première pour obtenir des innovations. Disons seulement que les deux activités sont également, mais différemment, utiles à nos sociétés. Les apports lipidiques (nutritionnels et non-nutritionnels), qui nous intéressent ici, peuvent faire, et le font d'ailleurs depuis longtemps, l'objet d'études dans les deux champs, parce que la pratique nutritionnelle est ce que l'on a nommé un « art chimique » quand la différence entre science et technologie était moins nette qu'aujourd'hui (1). Il y aurait d'ailleurs une histoire de la chimie à faire à partir des « arts chimiques », car ceux-ci semblent toujours avoir été au cœur du développement des sciences chimiques. Par exemple, le chirurgien français Ambroise Paré introduisit en 1560 le mot « émulsion » pour désigner des systèmes analogues au lait (du latin emulgere = traire), alors qu'il effectuait des études sur ce que nous nommerions aujourd'hui la « galénique », laquelle est un travail de « formulation ».

Ainsi, une émulsion est un mélange intime de deux liquides non miscibles, comme l'eau et l'huile, mais qui vont par des opérations spécifiques (agitation, mélange, ajout de quelques adjuvants) acquérir un aspect macroscopiquement homogène, mais microscopiquement hétérogène. L'un des liquides sera donc dispersé dans l'autre sous forme de fines gouttelettes. Le mélange demeure stable grâce à une

troisième substance appelée émulsifiant. Les émulsifiants, appelés parfois émulsionnants (ou émulgateurs), stabilisent l'émulsion. Ce sont le plus souvent des tensioactifs ou agents de surface.

Si les émulsions lipidiques issues des sciences et des technologies ont permis de développer des nouvelles voies d'apport nutritionnel et de formulation galénique, elles ont également entraîné chez les patients des perturbations métaboliques (2) ou encore des infections (3).

2. Les soins intensifs : contextualisation de l'étude

Selon la société suisse de médecine intensive, les soins intensifs sont à l'heure actuelle un aspect essentiel et indispensable de la médecine aiguë. La médecine intensive est un champ d'activité multidisciplinaire qui prend en charge des patients souffrant ou susceptibles de souffrir de la défaillance d'un ou de plusieurs systèmes organiques causée par une maladie, une intervention chirurgicale d'envergure ou un accident, et qui met en danger leur vie. Si les organes vitaux sont sévèrement touchés dans leur fonction, la médecine intensive se doit d'empêcher d'autres pertes de fonction par des mesures adaptées. Lorsque les fonctions d'un organe vital sont entièrement ou partiellement atteintes, la médecine intensive a pour mission de se substituer aux fonctions correspondantes aussi longtemps que nécessaire jusqu'à ce que l'organe endommagé soit rétabli et qu'il puisse à nouveau remplir son office de manière autonome.

Les changements qui interviennent dans le domaine de la prise en charge ou de l'évolution clinique du patient sont plus que quotidiens ; ils se présentent d'heure en heure, parfois de minute en minute. Le suivi de ces patients est assuré 24 heures sur 24 par des équipes médicales et infirmières spécialisées par des observations et des interventions immédiates voire continues, en vue de traiter ou et/ou d'éviter des complications.

Suite à l'agression dont ils sont victimes, les patients nécessitant des soins intensifs présentent tous un hypermétabolisme associé à une réaction catabolique intense entraînant une dénutrition avec perte de la masse maigre qui est de la masse corporelle métaboliquement active (4). En cas de dénutrition préexistante, la situation est encore aggravée et le risque d'une dénutrition est encore majoré lors de l'hospitalisation. Dans ce contexte, une étude prospective a rapporté que

les écarts entre la prescription et les apports nutritionnels par voie entérale étaient attribuables aux interruptions causées par l'intolérance digestive (27,7%), par les procédures d'assistance respiratoire (30,8%) ainsi que par les procédure de diagnostic (26.6%) (5). Selon les auteurs de l'étude précitée, les facteurs significativement associés à une baisse des apports nutritionnels étaient l'administration de médicaments vasoactifs, le cathétérisme veineux central et l'épuration extrarénale. Ceci suggère que la gravité de l'atteinte des fonctions vitales en soins intensifs conditionne l'apport nutritionnel. La faible attention portée à l'apport nutritionnel dans ces conditions peut être exacerbée par le fait que l'effet de la nutrition est difficile à visualiser sur le devenir d'un patient. Ceci est d'autant plus clair si l'on compare l'effet direct de la nutrition par rapport aux effets directs des catécholamines dans les cas de correction de l'hypotension. Ainsi, il apparaît que la nutrition en soins intensifs pourrait inconsciemment être considérée comme étant moins importante que les autres traitements fréquemment administrés. Sur la base de ces constats, un appui nutritionnel précoce fait partie des stratégies permettant de limiter l'importance des phénomènes de dénutrition (6). Cette idée est soutenue par la littérature (7-9) qui rapporte que la présence d'un protocole de nutrition en soins intensifs améliore l'état nutritionnel et réduit les évolutions défavorables, notamment par une diminution de la durée de ventilation mécanique assistée. Malheureusement, le protocole de nutrition introduit en 1999 au SMIA n'était pas connu ni appliqué. En février 2006, l'introduction d'un nouveau protocole de nutrition interdisciplinaire au SMIA (projet NUTSIA 1) a amélioré le processus de prise en charge nutritionnelle dans le service et semble en particulier avoir amélioré la détection des patients à risque (10). En pratique, le protocole NUTSIA favorise un dépistage des patients pour lesquels une

assistance nutritionnelle est requise ou à envisager et permet d'évaluer le degré de risque nutritionnel (cf. Annexe I, p.135). Selon l'aptitude du patient à s'alimenter, cette assistance nutritionnelle prend la forme de suppléments nutritifs oraux ou encore d'une nutrition artificielle entérale ou parentérale. Ces nutritions artificielles se présentent le plus souvent sous forme d'émulsions incluant glucides, acides aminés et lipides. Lors de nutrition artificielle, une surveillance sous forme de bilans métaboliques est régulièrement effectuée. La triglycéridémie en particulier fait l'objet d'un suivi régulier afin d'apprécier la tolérance du patient à l'émulsion lipidique.

3. Les lipides et leur physiologie

3.1. Nutrition parentérale

Les acides gras utilisés pour les émulsions des nutritions parentérales peuvent être classifiés en fonction de leurs caractéristiques structurelles comme la longueur de la chaîne carbonée, la présence et la position d'une double liaison carbone-carbone ainsi que leur configuration (c.-à-d. cis et trans) (11). Ils peuvent être soit saturés (pas de double liaison) soit insaturés avec une (mono-insaturés) ou plusieurs doubles liaisons (poly-insaturés). Les acides gras sont des constituants des triglycérides. En fonction de la longueur de leur chaîne R (cf. Figure 1, ci-dessous), on distingue les triglycérides à chaîne courte (SCT : < 8 carbones), à chaîne moyenne (MCT : 8-14 carbones), à longue chaîne (LCT : 16-20) et à très longue chaîne (VLCT : >20 carbones).

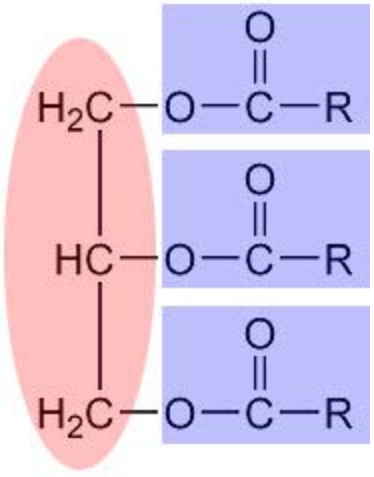


Figure 1: Triglycérides avec son glycérol (en rose) et ses acides gras (en bleu)

Les triglycérides, le cholestérol libre, le cholestérol estérifié, et les phospholipides font partie de la fraction lipidique des lipoprotéines (12). La fraction protéique de ces complexes macromoléculaires est constituée de diverses apolipoprotéines et permet l'acheminement des triglycérides, substrat énergétique, et du cholestérol, constituant indispensable à la physiologie des membranes cellulaires et à la synthèse des stéroïdes.

Ces lipoprotéines participent également au transport plasmatique des vitamines liposolubles. Les apolipoprotéines sont des cofacteurs enzymatiques et des ligands de récepteurs spécifiques. Le métabolisme des lipoprotéines est influencé de façon majeure par leur structure. Leur composition en lipides et en apolipoprotéines détermine leurs propriétés physico-chimiques et biologiques.

Il existe essentiellement quatre types de lipoprotéines :

– les chylomicrons, synthétisés par les entérocytes, transportant les triglycérides d'origine alimentaires,

– les very low density lipoprotein (VLDL), d'origine hépatique, transportant les triglycérides endogènes. La lipolyse intravasculaire des chylomicrons et des VLDL aboutit respectivement à la formation de reste de chylomicrons et des LDL,

– les low density lipoprotein (LDL) transportant le cholestérol vers les cellules périphériques. L'internalisation des LDL se fait surtout grâce à la reconnaissance de l'apoB100 par le récepteur aux LDL. Les LDL constituent la fraction la plus athérogène des lipoprotéines,

– les high denstiy lipoprotein (HDL) captant le cholestérol au niveau des cellules périphériques et permettant son retour au foie, d'où leurs propriétés antiathérogènes.

Contrairement à la nutrition entérale qui exploite une voie physiologique (cf. Figure 2, ci-dessous), la nutrition parentérale consiste à apporter des nutriments qui ne passent pas par les intestins et par conséquent, qui n'entraînent pas de synthèse de chylomicrons par les entérocytes (13).

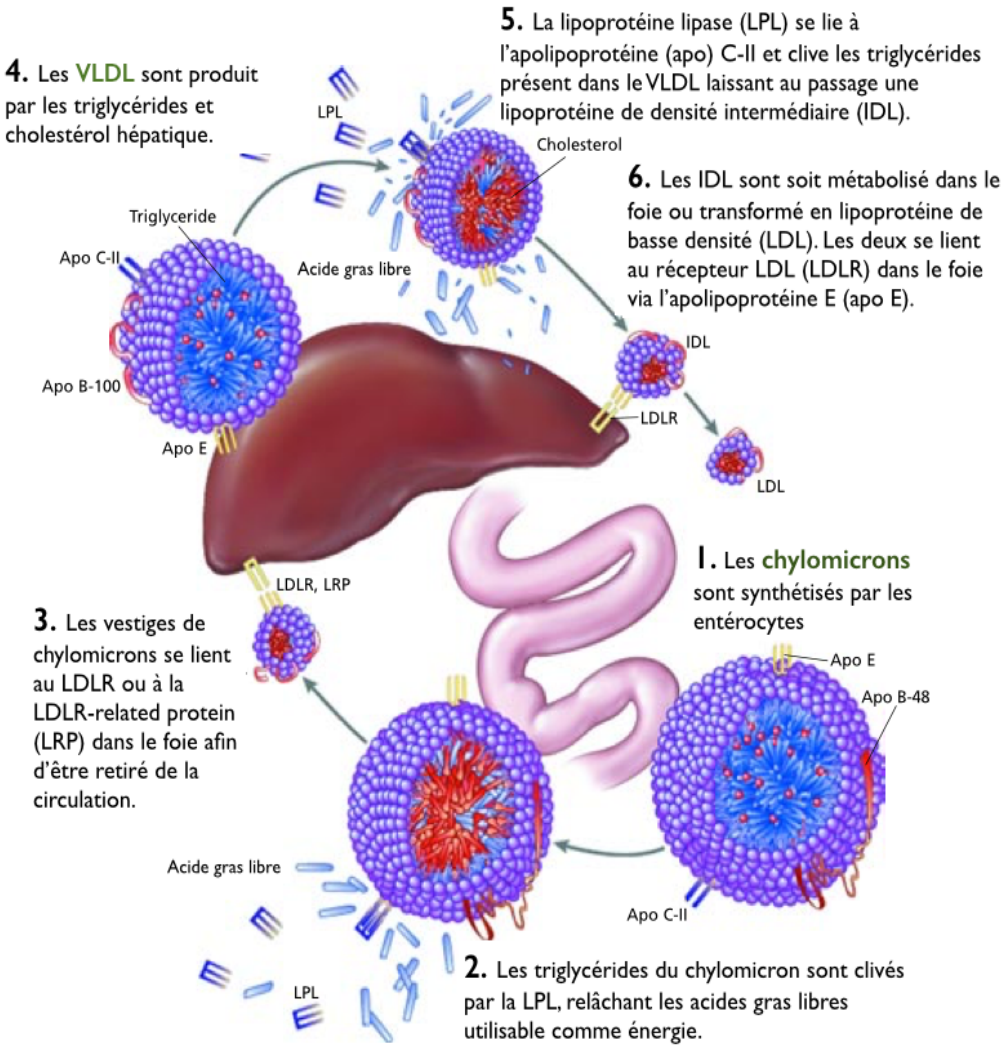


Figure 2: Cycles des lipides par voie entérale (14)

Les émulsions lipidiques présentes dans les nutritions parentérales ont été développées sur le modèle du chylomicron (15, 16). Elles sont utilisées pour fournir aux tissus des acides gras provenant des triglycérides. Ces particules d'émulsions sont différentes des chylomicrons, car elles ne contiennent pas

d'apolipoprotéines, mais dès leur perfusion dans la circulation sanguine, elles peuvent fixer des apolipoprotéines échangeables (p.ex. ApoCII, ApoCIII, ApoE etc...) par transfert à partir des HDL, acquérir des esters de cholestérol à partir des HDL et LDL circulantes et subir une hydrolyse intravasculaire d'une partie des triglycérides par la lipoprotéine lipase endothéliale (cf. Figure 3,ci-dessous) (13). Ces différentes étapes modifient leur composition et réduisent la taille des particules pour les convertir en particules résiduelles appauvries en triglycérides, mais enrichies en cholestérol estérifié.

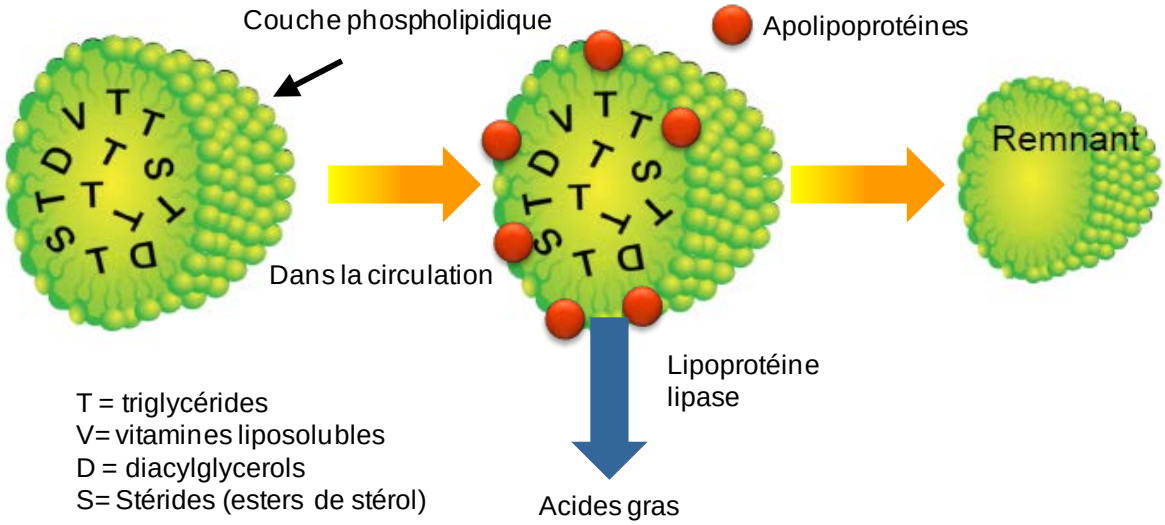


Figure 3: Modification des chylomicrons artificiels

La clairance (17) de ces particules résiduelles artificielles serait plus précoce que celles des restes de chylomicrons et passerait plutôt par une captation directe qui ne toucherait pas que le foie, mais également de nombreux tissus ou cellules. La composition en acides gras des nutritions parentérales est différente de celle des chylomicrons et varie entre les préparations existantes. Le métabolisme de ces acides gras peut donc être fortement différent en fonction de la préparation. La

composition en triglycérides et la taille des particules de l'émulsion (18, 19) influencent la capacité à fixer les apolipoprotéines, la lipolyse par la lipoprotéine lipase et surtout la captation des particules résiduelles artificielles. Ces phénomènes (19, 20) influencent non seulement la clairance plasmatique des acides gras perfusés, mais aussi la répartition des composants lipidiques entre les différents tissus.

La composition en acides gras des triglycérides formant les émulsions influence largement leur hydrolyse par la lipoprotéine lipase. Les MCT sont caractérisés par une plus grande solubilité dans la surface phospholipidique des chylomicrons artificiels que les LCT les rendant ainsi plus disponibles pour une hydrolyse par la lipoprotéine lipase (21). Les préparations ne contenant que des MCT sont donc hydrolysées nettement plus vite que des émulsions de à base de LCT. Dans les émulsions contenant un mélange des deux types de triglycérides (LCT et MCT), les MCT sont hydrolysés plus rapidement laissant les particules résiduelles progressivement enrichies en LCT. Ceci explique pourquoi le métabolisme des acides gras est largement dépendant des caractéristiques du rapport LCT/MCT des émulsions lipidiques (13, 21, 22).

3.2. Apports lipidiques

La complication métabolique majeure connue associée à la nutrition parentérale est l'hypertriglycéridémie. Dans une étude multicentrique, ce phénomène a été rapporté avec une incidence de 33% chez 260 patients recevant des lipides à raison de 0.83 ± 0.37 g/kg/jour (23). Même si la capacité d'élimination maximale des lipides chez un adulte est d'environ 3.8 g/kg/jour (15, 24), la littérature (23, 25)

n'a cessé de recommander au fil des années une diminution des apports lipidiques pour atteindre 0.7 à 1.5 g/kg/jour (11) dans l'optique de réduire les complications associées à l'administration intraveineuse d'émulsions lipidiques. Lorsque le débit de perfusion est supérieur à 0,15 g/kg/h, la clairance des lipides plasmatiques peut être dépassée. L'accumulation de triglycérides et de phospholipides entraîne alors des modifications des lipoprotéines et l'apparition de lipoprotéines atypiques, responsables de diverses manifestations pathologiques (26). Les émulsions lipidiques à 10 %, qui, à quantité de triglycérides égale, apportent plus de phospholipides que les émulsions à 20 %, sont déconseillées.

La surcharge en lipides intraveineux a plusieurs conséquences :

– leur captation par le système réticulo-endothélial provoque une accumulation de globules graisseux, observée dans le foie, la rate et les macrophages, et qui peut induire des perturbations immunitaires (27, 28) ;

– la surcharge en acides gras essentiels de la série n-6 favorise la synthèse de prostaglandines et de leukotriènes proinflammatoires ;

– l'apparition de phénomènes oxydatifs et l'augmentation de la peroxydation des acides gras polyinsaturés.

En particulier, l'apport excessif de lipides peut être responsable d'un syndrome d'activation macrophagique. Ce syndrome a été décrit initialement chez des nouveau-nés recevant des apports lipidiques de 4 à 6 g/kg/j, mais aussi des apports plus modestes de 1 à 2 g/kg/j (29). Il peut être déclenché par un syndrome infectieux. Il est polymorphe et associe : de la fièvre, des douleurs abdominales, des troubles respiratoires, une anémie, un ictère, une hépatosplénomégalie, des troubles de l'hémostase avec thrombopénie, une coagulation intravasculaire

disséminée pouvant entraîner des troubles hémorragiques. Le myélogramme met en évidence des images d'hémophagocytose.

En l'absence de traitement, ce syndrome met en jeu le pronostic vital. Le traitement repose sur l'arrêt des perfusions lipidiques associé à une corticothérapie de prednisone (2 mg/kg/j pendant cinq jours). La prévention associant un apport lipidique raisonnable, une surveillance de la turbidité du sérum, de la triglycéridémie et de la numération plaquettaire est primordiale. Enfin, des manifestations d'intolérance peuvent être observées lorsque l'émulsion lipidique est perfusée à un débit trop élevé : nausées, frissons, voire élévation thermique. Ces manifestations sont rapidement régressives à l'arrêt ou au ralentissement de la perfusion de lipides.

4. Paradigme de l'utilisation des émulsions aux soins intensifs

4.1. Nutrition parentérale : apports nutritionnels d'une émulsion

Dans la pratique courante aux soins intensifs du CHUV, il est préconisé de ne pas dépasser un apport parentéral ou entéral de lipides égal à 1 g/kg/jour.
Les nutritions parentérales du commerce ne correspondent pas toujours aux besoins des patients de soins intensifs. Le métabolisme lipidique chez les patients de soins intensifs peut être influencé tant par des facteurs exogènes qu'endogènes, et il n'est pas rare d'observer des dyslipidémies (2, 15, 23, 30, 31).

C'est la raison pour laquelle, la pharmacie du CHUV prépare des nutritions parentérales adaptées à ce type de patient. Il s'agit de l'ALISIA. Cette nutrition contient des émulsions lipidiques de type LCT/MCT qui sont plus facilement métabolisables (13, 21, 22). A noter que la quantité de lipides présents dans l'ALISIA est beaucoup plus faible que dans les spécialités du commerce.

4.2. Sédation au propofol : apport lipidique non nutritionnel d'une émulsion

Le propofol (2,6 di-isopropylphénol) résulte de recherches menées au début des années 1970 sur les dérivés alkyles du groupe phénol qui avaient démontré une activité hypnotique chez l'animal. La première publication rapportant son utilisation comme agent d'induction chez l'homme date de 1977 (32). Cependant très rapidement des réactions anaphylactoïdes dues au solvant (Crémophor EL) ont été rapportées. Il a donc été nécessaire de reconditionner la molécule dans une émulsion lipidique (1983). La commercialisation en Suisse pour les seringues prêtes à l'emploi, les flacons et les ampoules datent de septembre 1986.

Le propofol est l'agent sédatif le plus utilisé au service de médecine intensive adulte du CHUV intervenant dans 68% des séquences de sédation (33). En Europe, le propofol est le deuxième agent sédatif le plus utilisé derrière le midazolam avec une prévalence variable dans les séquences de sédation allant de 3 à 70% selon les pays mais correspondant à 35% en moyenne (34, 35). Ce dérivé phénolique très liposoluble se présente en solution dans une émulsion lipidique à 10% avec un rapport LCT/MCT de 100 :0 à 50 :50 (36, 37). Bien que la quantité des lipides perfusés avec le propofol soit généralement inférieure aux doses recommandées en nutrition parentérale, elle peut cependant contribuer à la surcharge lipidique entrainant l'hypertriglycéridémie (37). Par conséquent, la recommandation locale au SMIA en vue de limiter l'apport de lipides est d'utiliser la solution de propofol 2%. En cas d'hypertriglycéridémie chez les patients recevant de grandes quantités de propofol (p.ex. : les patients sous

neurosédation,etc.), il est recommandé d'utiliser une spécialité constituée d'une émulsion LCT/MCT.

Aucune corrélation entre l'utilisation de propofol et une augmentation de la triglycéridémie n'a pu être établie lorsque la période d'administration est inférieure à 72 heures (38). Par contre, une hypertriglycéridémie est fréquemment observée au-delà de 72 heures d'administration (39, 40). Pour une durée de sédation de 7 jours, l'élévation de la triglycéridémie serait d'environ 3 à 4 fois supérieure à la normale (40). Dans une étude prospective randomisée comparant midazolam et propofol 1%, Barrientos-Vega et al. (39) relèvent 20% d'hypertriglycéridémies (> 5.65 mmol/L) dans le groupe traité par propofol pour une durée moyenne de sédation de 140 heures (six jours environ). La normalisation de la triglycéridémie était obtenue dans les 72 heures après l'arrêt du traitement. Ainsi, si la littérature rapporte que l'hypertriglycéridémie est observée le plus souvent pour des doses élevées de propofol, elle n'est cependant pas directement corrélée à la quantité totale de lipides perfusés (37, 39, 41). Le mécanisme avancé pour expliquer les anomalies lipidiques observées sous propofol est celui d'un effet pharmacologique propre de la molécule qui bloquerait le transport et le métabolisme mitochondrial des acides gras (36, 42-44). En conclusion, que le phénomène soit lié à l'apport lipidique ou au mécanisme pharmacologique du propofol, une vigilance particulière s'impose lorsqu'une nutrition parentérale est administrée en même temps que le propofol : la quantité totale de lipides perfusés devrait tenir compte de celle apportée par l'émulsion du propofol.

5. Les complications associées à l'utilisation d'émulsions lipidiques

5.1. Influence des émulsions sur les triglycerides et l'hypertriglycéridémie

Selon une étude rétrospective de nature observatoire menée dans le service de médecine intensive adulte (SMIA), 1/3 des patients (n = 130) ont présenté au moins une fois une hypertriglycéridémie (> 2 mmol/L) et 1/10 avec des taux supérieurs à 3 mmol/L (45). À l'heure actuelle, les conséquences cliniques de l'hypertriglycéridémie sont encore mal connues même si des cas de pancréatite aiguë (2, 15, 23, 30, 31), de stéatose hépatique (4), de retard de réveil, de lipémie rétinienne (31), d'une majoration du risque infectieux par une perturbation du système réticulo-endothélial (2, 4), de coagulopathie (31, 38, 40), de perturbation neurologique (31) ou d'insuffisance respiratoire (2, 31, 46) ont été rapportés et largement discutés dans la littérature. Compte tenu des risques liés à l'hypertriglycéridémie, la littérature (47-49) recommande de surveiller régulièrement la concentration plasmatique de triglycérides au cours de la sédation prolongée avec le propofol.

5.2. L'émulsion en tant que forme galénique et ses coûts infectieux associés

Les infections nosocomiales primaires comptent pour approximativement 5-15% de toutes les infections acquises en milieu hospitalier et sont associées à une augmentation du séjour hospitalier et des coûts (50, 51) mais ne semblent pas associées à une augmentation de la mortalité globale (50). Les bactériémies primaires sont définies comme étant des infections systémiques documentées

sans source connue (51). Les patients de soins intensifs sont particulièrement à risque de bactériémie primaire à cause des cathéters veineux centraux implantés qui servent à l'administration d'émulsions lipidiques et/ou de médicaments (51-56). Cependant, la majorité d'entre elles sont maintenant évitables, notamment grâce à l'utilisation de compresses imprégnées de chlorhexidine disposée au site d'insertion du cathéter, ce qui diminue les risques pour les patients et permet de générer des économies (51, 57).

L'émulsion de propofol réunit toutes les conditions physicochimiques favorables à une croissance bactérienne. En effet, l'huile de soja, le glycérol, le phosphoglycéride d'œuf ainsi qu'un pH compris entre 4 et 7 favorise la croissance bactérienne. La littérature rapporte que de nombreux micro-organismes peuvent se développer dans ce milieu (58-62) et démontre, par exemple, que même à partir d'un faible inoculum de staphylocoques dorés (10-100 CFU/ml) à 34°C, 5 log sont retrouvés après 24 h (63).

Il existe cependant un délai de latence de 6h avant une augmentation exponentielle significative à 25°C. Après initiation de la croissance, le temps de doublement est de 3h à 25°C. Ceci explique pourquoi le délai d'utilisation du propofol, de sa préparation en seringue à la fin de son administration est fixé à 8h (53). Cependant les recommandations du fabricant ne sont pas toujours respectées dans certaines unités de soins intensifs et les délais dépassés.(53).

La littérature rapporte une incidence des contaminations durant la préparation des seringues de propofol variant de 4.8% à 11% (53-55, 64-68).

Des fièvres post-opératoires, des infections, des cas de sepsis, d'autres maladies potentiellement mortelles on été rapportées après des contaminations extrinsèques de propofol (52, 58, 61).

Afin de réduire le risque de contamination du propofol, de l'éthylène diamine tétra-acétate sodique (EDTA) a été ajouté à la formulation pour ces propriétés antimicrobiennes (69, 70). Il a en effet été démontré que 0.005% d'EDTA est efficace pour retarder certaines croissances microbiennes sans toutefois supprimer entièrement le risque de contamination (55). Les infections péri-opératoires constituent un problème médical sérieux avec un impact significatif sur la morbidité des patients, diminuent l'efficience hospitalière et augmentent les coûts de la santé. Les contaminations extrinsèques de propofol ont été identifiées comme étant un des facteurs de risque pour les infections associées aux soins de santé.

Le propofol formulé dans une émulsion contenant 100% de LCT pourrait provoquer une diminution de l'activité du système immunitaire mais cette possibilité reste malgré tout controversée (63).

En outre et selon la littérature, l'utilisation de seringues prêtes à l'emploi montreraient un plus faible taux de contamination des patients que les doses directement préparées au lit de ces derniers (71-75).

6. Justification du travail de thèse

Le lien entre l'utilisation des émulsions lipidiques et son incidence clinique étant avéré, un suivi quantitatif et qualitatif de l'administration semble aussi nécessaire qu'un suivi sur les bonnes pratiques d'administration. Une étude qualité sur l'administration de ces émulsions en milieu hospitalier n'avait encore jamais été effectuée. Ce travail avait pour but d'objectiver des stratégies d'utilisation des émulsions lipidiques dans un milieu de soins intensifs, qu'elles soient à visée nutritionnelle ou non.

7. Présentation du travail de thèse

Ce travail de thèse s'est déroulé en trois étapes distinctes, chacune d'elles donnant lieu à un article publié ou soumis à publication dans des journaux internationaux avec comité de relecture.

A la suite de ce 1er chapitre d'introduction, le chapitre II est consacré à la 1ère étape du travail sous forme d'un article intitulé «Does the type of parenteral lipids matter? a clinical answer in critical illness.».
L'objectif primaire avait pour but de comparer deux périodes distinctes. Pendant l'une des périodes, des patients de soins intensifs ont reçu une solution parentérale industrielle contenant des lipides structurés de type LCT/MCT et durant l'autre période une autre solution parentérale industrielle contenant des LCT n-9 FA (LCT+). L'objectif secondaire était d'évaluer la réponse métabolique de ces deux groupes de patients à ces deux types d'émulsion.

La 2ème étape constituant le chapitre III a fait l'objet d'un article dont le titre est «Hypertriglyceridemia: a potential side effect of propofol sedation in critical illness.» .

Cette étude a porté sur la prévalence, la sévérité et les facteurs de risques hypothétiques de l'hypertriglycéridémie dans une population de soins intensifs. De plus, la fréquence de suivi de la triglycéridémie a été déterminée.

Le chapitre IV est consacré à la troisième étape débouchant également sur un article et ayant pour titre «Example of a pharmacoeconomic modelling in an ICU environment: The case of prefilled propofol syringes to reduce primary bacteraemia in critically ill patients.».

Dans un contexte où les résistances aux bactéries à Gram négatif augmentent considérablement, contraignant les hôpitaux à utiliser de plus en plus d'antibiotiques à très large spectre, il nous a paru important d'évaluer la relation entre l'utilisation d'une émulsion lipidique préparée au lit du patient et les infections associées comparativement à une solution prête à l'emploi . Cette évaluation a été faite à l'aide d'un modèle pharmacoéconomique afin de déterminer si les coûts associés à l'utilisation de seringues prêtes à l'emploi compenseraient les coûts découlant d'une possible contamination en clinique. Pour cette réalisation, une estimation des probabilités de contamination entre les seringues préparées au lit du patient et les seringues industrielles prêtes à l'emploi a été réalisée. Par la suite, les coûts probables engendrés pour chaque type de seringue de propofol ont été exploré

CHAPITRE II

Article I

Does the type of parenteral lipids matter? a clinical answer in critical illness.

J.-C. Devaud [1, 2], M.M. Berger [3], A. Pannatier [1, 2], P. Voirol [1, 2], F. Sadeghipour[1, 2].

1. Service of Pharmacy, Lausanne University Hospital, Switzerland.

2. School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, Geneva, Switzerland.

3. Service of Adult Intensive Care Medicine & Burns, Lausanne University Hospital, Switzerland.

Résumé:

Contexte & Objectifs : Une altération du profil lipidique est fréquente chez les patients de soins intensifs, mais les évidences concernant l'impact de l'utilisation de différents types d'émulsions pour l'administration d'une nutrition parentérale aux patients sont rares. Cette étude avait pour objectif de comparer la réponse plasmatique des triglycérides (TG) à deux types d'émulsion lipidique industrielle : Un mélange de chaîne longue et moyenne de triglycérides (LCT/MCT) à des chaînes longues contenant des acides gras n-9 chez des patients de soins intensifs.

Méthodes : Dans cette étude rétrospective de nature observationnelle conduite dans un Service de soins intensifs multidisciplinaire, deux groupes ont été définis en fonction du type d'émulsion reçue. Les critères d'inclusion étaient les suivants : Patients ayant une durée de séjour sous nutrition parentérale ≥ 4 jours et ayant eu une (analyse globale) ou plus de 2 triglycéridémies. Les variables relevées étaient l'apport d'énergie, le type et la quantité de lipides nutritionnels, la dose de propofol, la quantité reçue de protéines et de glucose, les paramètres de laboratoires ainsi que tous les médicaments reçus. L'hypertriglicéridémie (hyperTG) a été définie comme étant > 2 mM.

Résultats : L'impact de ces émulsions a été analysé chez 187/757 patients (112 LCT/MCT et 75 LCT+). Les variables démographiques, les indices de sévérités, les catégories de diagnostiques et la mortalité ne présentaient aucune différence entre les deux groupes. Septante-sept patients (41%) ont présenté une hyperTG. Les deux groupes ont reçu des apports journaliers similaires d'énergie (1604 contre 1511 kcal/jour), de lipides (60 contre 61 g/jour) et de glucose (233 contre 197 g/jour). L'augmentation de la concentration des TG chez ceux qui ont reçu

l'émulsion de type LCT/MCT a été moindre que chez ceux ayant reçu les émulsions de type LCT+ (0.2 and 0.4 mM respectivement, $p < 0.05$).

Conclusion : Les émulsions de type LCT/MCT sont associées avec une augmentation moins prononcée des TG plasmatiques qu'avec les émulsions de type LCT+.

Abstract

Purpose*:* An altered lipid profile is common among intensive care unit (ICU) patients, but evidence regarding the impact of different fatty acid (FA) emulsions administered to patients requiring parenteral nutrition (PN) is scarce. This study aimed to compare the plasma triglyceride (TG) response to two types of industrial lipid emulsions: a mixture of long- and medium-chain triglycerides (LCT/MCT) or LCTs with n-9 FA (LCT+) in ICU patients.

Methods: In this retrospective observational study conducted in a multidisciplinary ICU: two groups were defined by the type of emulsion used. Inclusion criteria were as follows: consecutive patients on PN staying ≥ 4 days with one (global analysis) or two or more TG determinations. Recorded variables included energy intake, amount and type of nutritional lipids, propofol dose, glucose and protein intake, laboratory parameters, and all drugs received. Hypertriglyceridemia (hyperTG) was defined as TG > 2 mM.

Results: The impact of the emulsion was analyzed in 187/757 patients (112 LCT/MCT and 75 LCT+). The demographic variables, severity indices, diagnostic categories, and outcomes did not differ between the two groups. Seventy-seven patients (41%) presented hyperTG. Both groups received similar daily energy (1604 versus 1511 kcal/day), lipids (60 versus 61 g/day), and glucose intake (233 versus 197 g/day). The increase of TG concentration in those receiving the LCT/MCT emulsion was less than that in those receiving the LCT+ emulsion (0.2 and 0.4 mM, respectively, $p < 0.05$).

Conclusion: LCT/MCT emulsions are associated with a less pronounced increase of plasma TG levels than LCT+ emulsions.

Introduction

Critical illness is characterized by nutritional and metabolic disorders, resulting in increased muscle catabolism, fat-free mass loss, hyperglycemia, and hypertriglyceridemia (hyperTG) (76, 77). In patients with contraindications to enteral feeding or insufficient enteral feeding, parenteral nutrition (PN) is the standard care (11). Intravenous lipids are a vital component of PN as an important source of energy because they maintain integral components of cell membranes and prevent the development of essential fatty acid deficiency (78, 79). It has been demonstrated that PN is frequently associated with overfeeding and its deleterious consequences such as hyperglycemia, hyperTG, liver steatosis, endocrine dysfunction, impairment of immunity, infections, and increased mortality (11, 80, 81). The association between PN and morbidity is multifactorial and has often been suggested to be linked to the fat emulsions used (2, 11, 82). Although the evidence for this proposal has never been conclusive, particularly with the actual lipid emulsions, many centers limit the use of fat emulsions, especially when hyperTG is present (2, 11, 80).

The first available lipid emulsions contained only long-chain triglycerides (LCTs) (83). Some metabolic disorders have been published, and efforts at further developing and optimizing lipid emulsions have focused on replacing part of the LCTs with medium-chain triglycerides (MCTs) (84). Indeed, the fatty acids (FAs) composing emulsions do influence the clinical responses, depending on their chemical structure. Compared with LCTs, MCT-based emulsions are cleared more rapidly from the plasma (19, 82). Other benefits of MCTs include their less pronounced tendency for deposition in tissues and their favorable effect on protein metabolism (84, 85). Further advances include the development of structured lipids, which are metabolized even more efficiently than LCTs and MCTs (85).

Olive oil-based emulsions in which 80% of the LCTs consist of mono-unsaturated fatty acid (n-9 FA) were then developed (86): the latter have a limited impact on lipid metabolism. In the most recent emulsions developed, the LCTs and MCTs are progressively replaced by other fatty acids, particularly omega-3.

Having observed an increasing incidence of hyperTG after changing the industrial parenteral lipid emulsion in our intensive care unit (ICU), this study aimed to compare the metabolic responses to industrial PN solutions containing the LCT n-9 FA (LCT+) versus structured LCT/MCT lipids in critically ill patients.

Methods

This retrospective observational study was approved by the ethics committee of the Canton of Vaud and was conducted over a 50-month period (October 2008 to December 2013) in a 32-bed adult mixed ICU. Inclusion criteria were as follows: an ICU stay ≥ 4 days and < 18 days as well as plasma triglyceride (TG) level determination while on PN. Patients were excluded if there was less than 3 days of continuous PN or if the TG level was not determined during and after or before PN administration. HyperTG was defined as a plasma TG level > 2 mM, according to the current guidelines of the American Heart Association (87). Patients were grouped according to the type of PN received (see below).

Patient data

Patient data included age, admission weight, body mass index (BMI), type of admission (surgical or medical), severity of disease (SAPSII), and mortality during the ICU and hospital stay. All data were collected during the stay in order to have a dynamic view and to establish a temporal relationship with the type of lipid emulsion used. Nutritional data included intravenous and enteral energy, with

details of the quantity of lipids, carbohydrates, and proteins. The cumulative energy intake included nutritional (i.e., enteral nutrition (EN) and PN) and non-nutritional energy intake (i.e., propofol's lipid intake (mainly LCTs) and dextrose 5% perfusions). Laboratory data included the levels of alanine transaminase, aspartate transaminase, albumin, pancreatic amylase, direct and indirect bilirubin, gamma-glutamyl transferase, alkaline phosphatase, procalcitonin, prealbumin, and C-reactive protein.

Study periods

During the first period (2008 to 2011), the predominant industrial solution was an LCT/MCT emulsion (Structokabiven®, Fresenius Kabi, Oberdorf, Switzerland); while an LCT+ emulsion was used since 2011 (Olimel 5.7%®, Baxter AG, Volketswil, Switzerland). Some patients also received the CHUV local-compounded PN called ALISIA (ALImentation aux Soins Intensifs Adultes), which is an ICU patient adapted, concentrated (1230 mL), low-fat (20% of energy as LCT/MCT), high-protein (25% energy), and high-glucose solution (55% energy) (88, 89). This solution is recommended when PN lasts > 3 days. The compositions of these solutions are shown in Table 1.

Nutritional management

The nutrition protocol was based on the ESPEN guidelines, and the feeding protocol evolved over time as follows: Energy targets were 25–30 kcal/kg/day (medical and surgical conditions) during the first period, and they decreased to 20–25 kcal/kg/day during the second period (with downregulation in elderly and obese patients). Indirect calorimetry was recommended after 1 week. The protein target was 1.2–1.3 g/kg/day, and continuous EN was encouraged. Combined EN and PN was considered when EN was insufficient. Otherwise, PN was restricted to

gastrointestinal failure. Lipid profile monitoring was an integral part of the ICU nutrition protocol (blood sampling three times weekly at 6 a.m. for determination of TG and C-reactive protein levels). Non-nutritional intake was taken into account, and the sedation protocol was based on ESICM recommendations, discouraging the use of high-dose propofol (>4 mg/kg/h) while integrating daily sedation pauses. Overfeeding was defined as ≥ 28 kcal/kg in the absence of indirect calorimetric determination based on the large multicenter Spanish ICU study including 725 patients receiving either EN or PN (90).

All analyses were performed on a Cobas 8000 modular analyzer (Roche Diagnostics, Switzerland), except for prealbumin, which was determined on an Integra instrument (Roche Diagnostics, Switzerland). Enzymatic methods were used to determine TG levels (GPO-PAP), and an immunoturbidimetric assay was used for the determination of albumin and C-reactive protein. Pancreatic amylase was determined by an immunoinhibition assay, and an electrochemical immunoassay was used for procalcitonin antigen detection. The hospital's Laboratory of Clinical Chemistry is ISO 15189:2012 certified.

Data collection and analysis

Data were extracted from the clinical information system (CIS) MetaVision (iMDSoft®, version 5.45.5403, Tel Aviv, Israel). The CIS was customized to provide detailed composition information and quantities of the enteral and parenteral feeding solutions, including the respective amounts of LCTs and MCTs (91). It was customized to show the total energy with detailed information including non-nutritional substrate intake.

The data and results are presented as medians and interquartile ranges or as number of subjects and percentage. Two-way analysis of variance and linear

regression were used for analysis with the software programs R language (R Foundation, version 2.10.0) and JMP V5.1 (SAS Institute, Cary, NC, USA). Statistical significance was considered at the level of $p < 0.05$.

Results

During the study period, 10,656 patients were admitted to the ICU, of whom 757 (7%) were on PN and eligible for the study based on the length of stay. Altogether, 228/757 patients (30.1%) presented at least one hyperTG during their PN, but there was no significant difference between the LCT/MCT and LCT+ groups ($p = 0.53$). Only 187/757 patients could be analyzed for TG changes during PN due to missing/misplaced TG determinations during their ICU stay. The clinical characteristics of the 112 (60%) patients on LCT/MCT PN and the 75 (40%) patients on LCT+ are summarized in Table 2. In the LCT/MCT group, there was more combined nutrition and a shorter length of stay ($p < 0.0001$) (Table 2).

Evolution of plasma TG

Among patients with at least two TG determinations, including at least one TG determination during and one before or after PN, 77/187 patients (41%) presented at least one hyper during their PN. The incidence did not differ between the two groups ($p = 0.66$). The increase of TG level was significantly greater in the LCT+ group than in the MCT/LCT group (Table 2) and is illustrated in Fig. 1. However, in patients who were shifted from a commercial PN to ALISIA, the TG level decreased; this change in TG level differed significantly from both industrial PNs (Table 3). In cases of excessive lipid delivery (lipids > 1.5 g/kg), there was a trend to more pronounced increases in plasma TG levels, although the change was not significant ($p = 0.07$) in either group.

Feeding

The duration of PN was similar in both groups. The median intravenous energy deliveries were 24.7 kcal/kg/day [18.3; 28.3] and 21.9 kcal/kg/day [18.6; 25.3] for the LCT/MCT and LCT+ groups, respectively (p = 0.0897). Most measured values did not differ between the two groups; the lipids, intravenous and/or enteral energy, and carbohydrate as well as protein delivery remained within the recommended ranges (Table 4).

Thirty-two patients received more than 28 kcal/kg/day, the target being based on indirect calorimetry in three patients (Table 2). Overfeeding was observed less often in the LCT+ group (5/7) than in the LCT/MCT group (20/25) (p = 0.0027). Among the patients with overfeeding, one patient in the LCT/MCT group and two patients in the LCT+ group were on strict PN, while the other patients were on combined nutrition. In addition, a positive correlation was observed between lipid delivery and propofol dose (r^2 = 0.28; p < 0.0001), and a negative correlation was found between enteral energy (kcal/day) and intravenous energy (kcal/day) (r^2 = 0.37; p < 0.0001), reflecting progression towards EN.

There were no significant differences between the levels of aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma-glutamyl transferase, C-reactive protein, total bilirubin, direct bilirubin, or prealbumin between the two groups (Table 4).

Discussion

The main finding in our study was that PN containing structured lipids of LCTs and MCTs did not impact the TG profile as much as PN containing LCTs alone, when delivered at similar fat doses. This finding might reflect a faster clearance by the lipoprotein lipase, which hydrolyzes MCTs more rapidly and completely than LCTs alone (19). It has been proposed that MCTs, because of their rapid and rather

complete oxidation, are associated with a lower risk of developing hyperTG than LCTs alone (2). However, this hypothesis has remained controversial (92) probably because these studies had no clear TG baseline and investigated the incidence of hyperTG rather than changes in the TG profile. The small size of the studies and the low patient numbers may also explain the limited findings in the literature (82, 93).

Our ICU feeding protocol was based on the ESPEN guidelines (11, 94), which recommend 1.2 to 1.5 g/kg/day of protein/amino acids. Thus, the protein delivery was similar to that observed in other European studies (95, 96). It is recommended that the glucose delivery should not exceed 6 g/kg/day and that the lipid supply should not exceed 1.5 g/kg or 35% of the total energy input (81). These recommendations were followed in our cohort.

As our energy target recommendations decreased during the second period (from 25–30 kcal/kg/day to 20–25 kcal/kg/day), the LCT+ emulsion was chosen because of its higher amino acid content in order to maintain an adequate nitrogen intake. This modest reduction in energy resulted in a reduction of delivery of approximately 100 kcal/day. Despite this reduction, there were larger (but not more frequent) increases in the TG level; however, the difference in the lipid profile cannot be attributed to a higher substrate and energy delivery. Even the propofol intake was similar, thus excluding a factor that might favor hyperTG (89).

We observed that the LCT/MCT group had a significantly shorter hospital stay of 2.4 days. However, a meta-analysis by Wirtitsch *et al*. did not demonstrate any statistically significant reduction in the length of hospital stay in any of the emulsion groups studied (93). Meanwhile, Bauer *et al*. showed that the length of hospital stay was significantly ($p = 0.0022$) reduced by 2.5 days in the group that

had benefited from early combined EN and PN to fulfil the target (97). There was no difference between our two groups for patients on combined nutrition, nor any difference in death rate, but mortality is multi-factorial in the ICU. The ALISIA substrate composition is close to the optimal PN recommendations, with only 20% of energy as fat (79, 82, 83, 95, 98). Its use was associated with a decrease in the plasma TG level, confirming the impact of a lower proportion of fat. Since parenteral fat intake is known to exacerbate hyperTG during acute illness (2, 15), we investigated individual fat intake in those patients presenting hyperTG. We observed that the guidelines for parenteral fat intake (11) (i.e., 0.7–1.5 g/kg/d) were respected.

Overfeeding, with glucose and/or fat by enteral or intravenous routes, is a common cause of hyperTG (99); however, in our cohort, overfeeding was an exception. Indeed, to prevent overfeeding, all patients were monitored daily against a standard energy target, which was verified by indirect calorimetry in several cases. Our system demonstrated the cumulative carbohydrate dose from both enteral and intravenous routes, thereby preventing the administration of doses and proportions known to induce *de novo* lipogenesis (11, 100) and reducing the risk of *de novo* lipid synthesis (101). Our results showed that reducing the energy target in the second period contributed to a lower rate of overfeeding.

Although cases of acute pancreatitis, fatty liver, delayed awakening, retinal lipemia (2, 15, 23), and elevated mortality, particularly in association with hypocholesterolemia (102), have been described, the clinical consequences of acute and transient hyperTG have not been investigated to date. An increased risk of infection by disruption of the reticuloendothelial system (2, 103), coagulopathy (38), neurological disturbance, or respiratory failure (2) also have been reported, none of which occurred in our patients. Therefore, further randomized controlled

trials are needed to determine which alternative PN emulsion should be used in critically ill patients to improve lipid metabolism and clinical outcomes, (104).

Limitations of the study

The principal limitation of this retrospective exploratory observational study is the modest size of the cohort, which limits the analysis (n = 187 with 41% hyperTG). The low number was due to the twice weekly monitoring protocol not being systematically applied, leading to many patients having only one TG determination available. However, the relatively small number of observations has to be weighed by the fact that our cohort included very sick patients with a median stay of 11 days and 15% ICU mortality (26% hospital mortality) and that the ICU's computerized database contains very complete metabolic information.

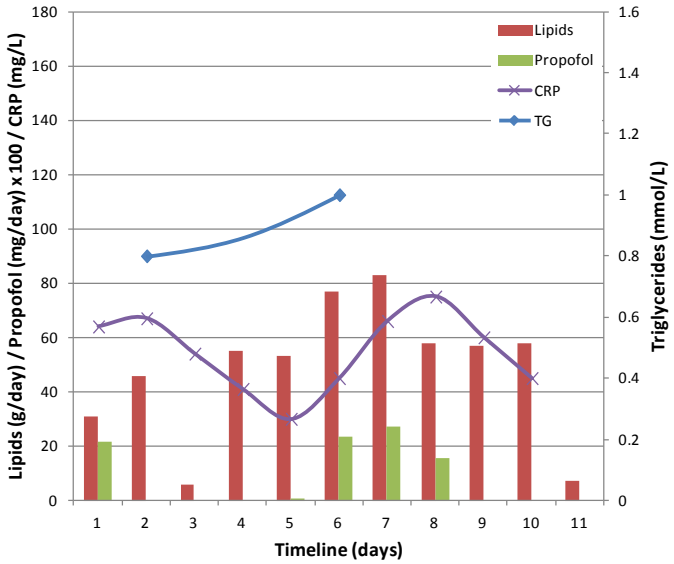
Another limitation of this study is that a mixture of both types of fatty acids was used in several cases due to the clinical use of propofol (an LCT emulsion), as shown in both depicted cases. Therefore, the observed changes in TG levels were not due to a unified process. Another limitation is the wide spectrum of pathologies present and presumably the genetic characteristics in the cohort, both of which modulate the metabolic responses to feeding. In the absence of more information, these aspects cannot be explored.

Conclusion

HyperTG is frequent during critical illness. In addition to the previously identified factors associated with hyperTG, the present study demonstrated that the type of fat emulsion directly influences the TG profile. The MCT-containing PN was associated with a lower impact on the plasma TG level than the LCT+ emulsion in this cohort of critically ill patients. Therefore, the TG levels of critically ill patients

should be regularly monitored, probably before the initiation of PN and then twice weekly during PN or during propofol sedation. Furthermore, more extensive knowledge regarding the effects of various types of emulsions on outcomes such as the TG profile, length of hospital stay, and clinical consequences of hyperTG is necessary.

A



B

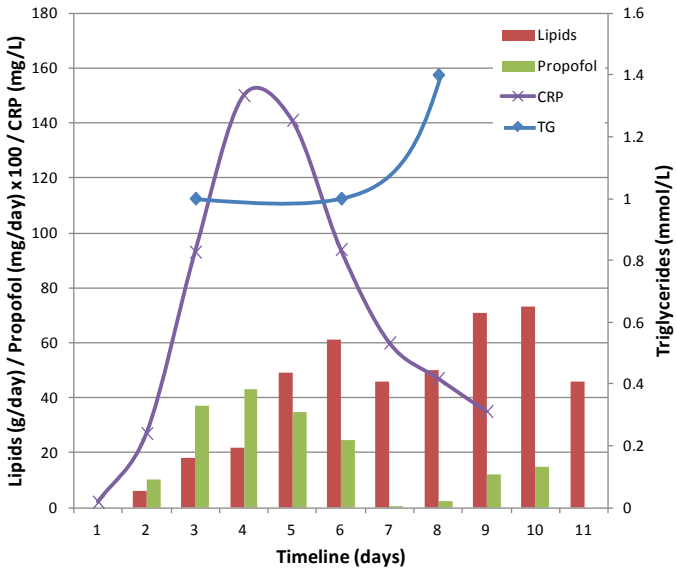


Fig. 1 Analyses of plasma TG and C-reactive protein levels over 11 days in patients receiving PN containing MCT/LCT (A) or LCT+ (B), with the total daily dose of fatty acids (from PN and propofol) indicated. The patients presented increases of 0.2 mM and 0.4 mM TG, respectively.

Table 1 PN compositions

Parameter	Structokabiven[a] (64% LCT/36% MCT)	Olimel 5.7%[b] (100% LCT)	ALISIA[a] (50% LCT/50% MCT)
Energy (kcal/L)	1054	1028	1399
Lipids (g/L)	38	40	27
Amino acids (g/L)	51	56.9	86
Glucose (g/L)	127	110	203

[a] soya and coconut oil

[b] soya and olive oil

Table 2 Patient characteristics and outcome variables

Variable	LCT/MCT (N = 112)	LCT+ (N = 75)	p
Age (years)	67.5 (58.8–76)	64 (55.5–74)	NS
Preadmission weight (kg)	75 (65–87)	78 (68.5–86)	NS
Body mass index (kg/m^2)	24.7 (23.2–28.8)	25.8 (23–29.6)	NS
Women (%)	28.6% (32)	26.6% (20)	NS
SAPS II	48 (39–60)	50 (39.5–60.5)	NS
Medical/surgical ratio	28.8%/73.2% (30/82)	30.1%/69.8% (23/52)	NS
Propofol dose during PN (mg/kg/d)	13.0 (3.3–30.4)	9.4 (1.4–32.4)	NS
Patients on combined EN+PN (N)	77	5	<0.0001
TG profile			
TG concentration (mM) before PN	1.5 (1.1–2.2)	1.4 (1.1–1.8)	NS
TG concentration (mM) during PN	1.6 (1.1–2.2)	1.7 (1.2–2.3)	NS
Change of TG concentration (mM)	0 (-0.3–0.4)	0.2 (-0.1–0.7)	0.01297
Outcome			
Length of ICU stay (days)	10.6 (8.7–13.7)	13 (9.1–16.1)	0.0292
Combined nutrition (days)	2 (1–4)	2 (0–4)	NS
Number of patients receiving ≥ 28 kcal/kg/day	22% (25)	9% (7)	0.0223
ICU mortality (%)	14.3% (16)	16% (12)	NS
Hospital mortality after discharge from ICU (%)	25.9% (29)	26.6% (20)	NS

Results are expressed as median (interquartile range) or as percentage (number of subjects). *TG* triglyceride, *PN* parenteral nutrition, *EN* enteral nutrition, *NS* not significant.

Table 3 Changes in TG concentration under the different PN types

Type of emulsion	Change of TG concentration (mM)	N	p
LCT+	0.4 (0–1)	71	
LCT+ & ALISIA	0.2 (0.02–0.72)	10	0.0251
LCT/MCT	0.25 (-0.1–0.7)	66	
LCT/MCT & ALISIA	-0.05 (-0.4–0.4)	40	

Results are expressed as median (interquartile range).

TG triglyceride, *PN* parenteral nutrition, *N* number of patients.

Table 4 Details of feeding, outcomes, and other laboratory results

Parameter	LCT/MCT (N = 112)	LCT+ (N = 75)	p
Feeding			
Days to first PN (days)	2 (2–4)	2 (1.5–4)	NS
PN days (n)	6 (4–7.25)	6 (5–8)	NS
Prescribed energy (kcal/day)	1800 (1700–2000)	1800 (1500–2000)	NS
Recommended target (kcal/day)	1875 (1625–2175)	1716 (1507–1892)	0.0006
Harris & Benedict predicted REE (kcal/day)	1497 (1331–1703)	1557 (1346–1744)	NS
Measured substrate and energy delivery during PN			
Energy delivery (kcal/day)	1604 (1231–1827)	1511 (1225–1771)	NS
Protein (g/day)	84 (72.1–94.8)	85 (73–94.8)	NS
Protein (g/kg/day)	1.3 (1.1–1.5)	1.3 (1.1–1.4)	NS
Lipids (g/day)	60 (50–71)	61 (50–68)	NS
Lipids (g/kg/day)	0.9 (0.8–1.1)	0.89 (0.7–1)	NS
Glucose (g/day)	233 (213–261)	197 (176–222)	NS
Glucose (g/kg/day)	3.6 (3.2–3.9)	3.1 (2.7–3.4)	NS
Aspartate transaminase (UI/day)	49.5 (32.4–80)	57.5 (33–104)	NS
Alanine transaminase (UI/day)	39.75 (25.8–67.3)	42.5 (24.6–96.3)	NS
Alkaline phosphatase (UI/day)	117 (78–164)	124.5 (92.1–205.6)	NS
Gamma-glutamyl transferase (UI/day)	129 (65–259.8)	148 (81.4–251.6)	NS
C-reactive protein (UI/day)	120.5 (71.5–165.3)	121 (67.3–162)	NS
Total bilirubin (UI/day)	18 (14.5–49.3)	28.25 (15.6–53)	NS
Direct bilirubin (UI/day)	26 (14.5–53)	27 (17–51)	NS
Prealbumin (UI/day)	0.1 (0.1–0.1)	0.09 (0.1–0.1)	NS

Results are expressed as median (interquartile range).

PN parenteral nutrition, *REE* Resting energy expenditure, *NS* not significant.

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CHAPITRE III

Article II

Hypertriglyceridemia: a potential side effect of propofol sedation in critical illness.

J.-C. Devaud [1, 2], M.M. Berger [3], A. Pannatier [1, 2], P. Marques-Vidal [4], L. Tappy [5], N. Rodondi [6], R. Chiolero [3], P. Voirol [1,2].

1. Service of Pharmacy, Lausanne University Hospital, Switzerland.

2. School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, Geneva, Switzerland.

3. Service of Adult Intensive Care Medicine & Burns, Lausanne University Hospital, Switzerland.

4. University Institute of Social and Preventive Medicine, University of Lausanne, Switzerland.

5. Department of Physiology, University of Lausanne, Switzerland.

6. Department of Ambulatory Care and Community Medicine, University of Lausanne, Switzerland.

Résumé :

But : L'hypertriglycéridémie (hyperTG) est fréquente chez les patients de soins intensifs (SI) mais les connaissances sur les facteurs de risque de l'hyperTG aux SI sont rares. La présente étude visait à identifier les facteurs de risque favorisant la survenue d'une hyperTG chez les patients nécessitant un séjour prolongé.

Méthodes : Étude observationnelle prospective en réanimation médico-chirurgicale d'un hôpital universitaire. Tous les patients consécutifs séjournant ≥ 4 jours ont été inclus sur une période de sept mois. Les facteurs de risque potentiels ont été enregistrés : pathologie, apport énergétique, quantité et type de lipides nutritionnels, apport de propofol, ingestion de glucose, paramètres de laboratoire et médicaments. Ces derniers (niveaux de triglycérides (TG), cholestérol, HDL-cholestérol) ont été évalués 3 fois par semaine. Les associations entre les niveaux de la TG et les facteurs de risque potentiels ont été évaluées par régression linéaire.

Résultats : Sur 1301 admissions consécutives, 204 patients ont été inclus et 79 (38,7 %) ont présenté une hyperTG. L'apport du propofol lui-même (mg/kg/j) et des lipides du propofol montraient la plus forte corrélation avec les taux plasmatiques de TG (r^2 = 0,161 et 0,148 respectivement, $p < 0,05$). Aucune association significative n'a été trouvée avec les lipides nutritionnels. La corrélation entre dose de propofol (mg/kg/j) et taux de triglycérides était toujours présente après exclusion des sujets souffrant de pancréatite aiguë, septicémie ou les deux.

Conclusion : L'hyperTG est fréquente en réanimation, mais elle ne se produit pas lorsque les lignes directrices en matière de nutrition et de sédation sont suivies. À l'inverse, nos résultats suggèrent que chez les patients recevant de fortes doses de propofol, les taux plasmatiques de TG doivent être surveillés au moins deux fois par semaine. Les

conséquences cliniques du propofol sur l'hyperTG devraient faire l'objet d'études plus approfondies.

Abstract:

Purpose: Hypertriglyceridemia (hyperTG) is common among intensive care unit (ICU) patients but knowledge about the hyperTG risk factors is scarce. The present study aimed at identifying risk factors favoring its development in patients requiring prolonged ICU treatment.

Methods: Prospective observational study in the medico-surgical ICU of a University teaching hospital. All consecutive patients staying ≥4 days were enrolled. Potential risk factors were recorded: pathology, energy intake, amount and type of nutritional lipids, intake of propofol, glucose intake, laboratory parameters and drugs. Triglycerides (TG) levels were assessed 3 times weekly. Statistics: 2-way ANOVA, linear regression with potential risk factors.

Results: Out of 1301 consecutive admissions, 220 patients were eligible, of which 99 (45%) presented an hyperTG (triglycerides > 2 mmol/L). HyperTG patients were younger, heavier with more brain injury and multiple trauma. Intake of propofol (mg/kg/h) and lipids' propofol had the highest correlation with plasma TG (r^2=0.28 and 0.26 respectively, both p<0.001). Infection and inflammation were associated with the development of hyperTG (CRP r^2=0.19, p=0.004). No strong association could be found with nutritional lipids or other risk factors. Outcome was similar in normo- and hyperTG patients.

Conclusion: HyperTG is frequent in the ICU but is not associated with adverse outcome. Propofol and accompanying lipid emulsion are the strongest risk factors. Our results suggest plasma TG should be monitored at least twice weekly in patients on propofol. The clinical consequences of propofol related hyperTG should be investigated in further studies.

Introduction:

Hypertriglyceridemia (hyperTG) is a common metabolic complication in critical illness (2, 39) but data on its incidence, risk factors and impact on outcome are scarce. The main causes of hyperTG are either genetic or associated with a secondary pathology such as pancreatitis (105), sepsis (106), obesity(107), liver failure(15, 80), chronic renal failure (2, 15, 23), alcohol consumption (108) or type 2 diabetes (109, 110). The type of illness influences the lipid profile, the magnitude of the changes being proportional to the severity of the disease (111); patients with infections are particularly prone. Despite unclear multifactorial etiology, high lipid levels are considered as a source of complications in intensive care unit (ICU) patients (2, 15, 23) and should be prevented.

Since the mid 80s, overfeeding has been identified as a potential cause of multiple metabolic disorders. The ESPEN Guidelines recommend a daily energy intake of 25-30 kcal/kg/day in medical and surgical ICU patients, and even less in the early phase (11): the daily fat intake should not exceed 0.7-1.5 g/kg to prevent fat overload (11). Similarly exceeding a cumulative glucose intake of 5 g/kg/day should be avoided to prevent de novo lipogenesis (11). Despite these recommendations, a multicenter study reported a 33% incidence of hyperTG, defined as plasma triglycerides (TG) >3 mmol/L, among hospitalized patients receiving a parenteral daily fat intake of 0.83 ± 0.37 g/kg (23). The type of lipid also influences TG levels: medium chain triglycerides (MCT) and omega-3 lipid emulsions are alternatives to long chain triglycerides (LCT) (15, 80), even if the metabolic advantages compared to LCT emulsions remain debated (92). Contrary to parenteral fat intake, enteral fat has rarely been associated with hyperTG (112). Critically ill patients frequently require sedation. One of the most popular drugs is propofol which is emulsified in lipid solutions. Some small studies suggest that high doses of propofol may play a key role in hyperTG (37, 39). Apart from feeding and propofol, several drugs do influence lipid levels: statins (107)

and insulin (2, 109) decrease TG levels, while heparin (113, 114), β-adrenergic catecholamines (115) and corticosteroids (2) have been shown to induce hyperTG.
The present study aimed to determine the prevalence, severity and risk factors of hyperTG in a population of critically ill patients in order to generate clinical etiological hypotheses and determine whether TG should be monitored in the ICU.

Patients and methods:

This prospective observational study approved by the ethic committee of the Vaud Canton was conducted over a 7-months period (March to October 2009) in a 32-bed adult mixed ICU. Individual consent was waived as the lipid profile monitoring was an integral part of the ICU nutrition protocol (blood sampling 3 times weekly at 6 a.m. for determination of TG levels and 1 time weekly for Cholesterol, HDL-cholesterol, C-reactive protein (CRP), albumin and thransthyretin. Inclusion criterion was an ICU stay ≥ 4 days. Exclusion criteria were: only one determination of TG during the stay and patients on oral feeding. Hypertriglyceridemia was defined as a plasma TG level > 2 mmol/L (87), severe hyperTG being defined as TG > 5 mmol/L. Patients were allocated to 2 groups according to the peak TG level either to normo- or hyperTG groups. The patients were classified according to predefined diagnostic groups, i.e. sepsis (severe sepsis and septic shock (116) on admission or at the time of the hyperTG), acute pancreatitis, diabetes (type I and II), chronic renal failure, use of statins before and during hospitalization with specification of preexisting dyslipidemia. The control group was constituted by patients without these pathologies.
Data were extracted from the the clinical information system (CIS: MetaVision® iMDSoft, version 5.45.5403, Tel Aviv, Israel), which is customized to provide detailed composition and quantities of the enteral and parenteral feeding solutions including the respective

amount of LCTs and MCTs (91). The non-nutritional substrate intakes were also integrated in the computations, whether coming from glucose 5%, or the propofol lipid emulsions. The cumulative energy intake included nutritional (i.e. enteral = EN, and parenteral nutrition = PN) and non-nutritional energy intake (i.e. glucose or lipid vehicle).

Patient data included age, admission weight, ideal body weight (IBW), Body Mass Index (BMI), type of admission (surgical or medical), diagnosis and mortality (ICU and hospital). Recorded medications included statins (type and dose), heparin, insulin, catecholamines, corticosteroids (hydrocortisone equivalents) and propofol (mg/d and mg/kg/h). Propofol is delivered under 3 forms: 2% solutions for continuous sedation (Disoprivan®, Astra Zeneca, Zug, Switzerland; Propofol MCT Fresenius®: Fresenius Kabi, Oberdorf, Switzerland), and 1% solution for short procedures (Disoprivan®). The differences in fat content are integrated in the CIS.

All plasma TG were recorded to enable the calculation of “delta-TG” (difference between the lowest and the highest TG value), including in normoTG patients: the delta-TG value hence differs from the peak value. Only the highest TG value was considered for the analysis of the temporal relationship with specific risk factors.

Laboratory data included ALT, AST, albumin, pancreatic amylase, direct bilirubin, creatinine, γ-GT, glycemia, lipase, alkaline phosphatase, procalcitonin, CRP, thromboplastin time, urea. Triglycerides/L, cholesterol /Land HDL-cholesterol/L were analyzed as independent variables.

Clinical management: The ICU’s feeding protocol recommends an energy target of 25-30 kcal/kg/d for medical and surgical conditions respectively (with down regulation in elderly and obese) and indirect calorimetry after 1 week (117). Continuous EN is encouraged, PN being limited to gastrointestinal failure: all feeding solutions contained either MCT/LCT mixtures or structured lipids (no fish oil). The sedation protocol based on the

recommendations of the European Society of Intensive Care Medicine discourages the use of high dose propofol (>4 mg/kg/h) while integrating daily sedation pauses. The ICU glucose control protocol is nurse driven and aims at blood glucose values between 6 and 8 mmol/L (determined by blood gas analyzer).

Analytical methods: Enzymatic methods were used to determine triglycerides (GPO-PAP), cholesterol (CHOD-PAP), HDL-cholesterol (CHOD-PAP, HOMOGENE PEG). For others determinations, standards methods were used: the laboratory is ISO certified.

Statistical analysis: Results were expressed as median and interquartile range or as number of subjects and percentage, as well as mean ±SEM in fig. 1. Variables were tested for normality, and TG values were found to be non-normally distributed, and therefore log values were used for further analysis. The factors associated with hyperTG were further analyzed using simple and multiple linear regressions. The groups of patients at risk were compared post hoc to the control group with the Dunnett's test. The odds ratios for hyperTG and the 95 percent confidence intervals were calculated using the method described by Armitage and Berry (118). Statistical packages were: JMP V8.1 (SAS Institute, Cary, NC, USA) and R (R Foundation, version 2.15.1) an open source software. Statistical significance was considered at the level $p < 0.05$.

Results:

During the study period, 1301 patients were admitted to the ICU, of whom 308 (23.7%) were eligible for the study: 88 patients were excluded due to eating regular meals (n=50), and 38 patients with only one TG determination.

The clinical characteristics of the 220 patients are summarized in Table 1. All patients required mechanical ventilation, and stayed for 10.4 days as a median in the ICU. Ninety nine patients (45%) developed hyperTG. The hyperTG patients were younger, had lower SAPSII scores, and stayed longer in the ICU while mortality did not differ from normoTG. The pathologies were unevenly distributed with more cardiac pathologies and less trauma in the normoTG group (p=0.04). Among the predefined risk categories, those poorly represented were grouped (n=11): diabetes (n=7), renal failure (n=3), pancreatitis (n=1). Septic patients (n= 124) were observed in all diagnostic categories and were overrepresented in the hyperTG group (n=75; 76%). Altogether 70 patients received statins either before or during their stay, 12 for dyslipidemia, 11 after an acute myocardial infarction, and the others for unclear reasons.

Feeding: Twenty-four hours before the peak TG value, 136 patients (61.8%) were under EN, 36 (16.4%) under PN, 29 (13.2%) received combined nutrition (i.e. EN+PN) and 19 were unfed. Energy intakes were on the hypocaloric side (median 16.8 kcal/kg/day). The hyperTG group received significantly more fat, while remaining within recommended ranges: energy and glucose intakes did not differ. The higher fat load in the hyperTG group resulted mainly from propofol fat.

Plasma Triglycerides: TG values varied during the stay in all patients, but varied significantly more in those patients developing hyperTG. The latter patients started with higher TG reference values, although the majority of these values were within normal ranges.

HyperTG occurred after 7 days as a median, and after 4 days on higher dose propofol. Fig. 1 shows the significant differences in propofol delivery between the 2 groups, causing a significant larger fat delivery (daily propofol and fat dose: r^2=0.222, p<0.0001).

While total cholesterol did not differ significantly, HDL-cholesterol was lower in the hyperTG patients (0.46±0.30 0.79±0.37 mmol/L: p<0.0001). Low total and HDL-cholesterol were both associated with hospital mortality (p < 0.05).

Pathologies and drugs:

No significant relationship between co-medications (insulin, heparin, catecholamines, corticosteroids or other drugs) and TG levels was observed.

Among patients on statins, 26 (37.1%) developed hyperTG versus 48.7% in those not receiving statins (p=0.108, ns). Patients on statins received less propofol than those without. They presented significantly fewer infections (41.4% versus 63.3% p=0.0023), but no difference in mortality (9% versus 10% ICU mortality).

Table 2 summarizes the results of the single regression analysis between TG levels and the various risk factors. Correlation between plasma TG and total cholesterol was fair (r^2 = 0.41, p<0.001).

Infection, inflammation (CRP) and propofol were significantly associated with hyperTG, both by single and multiple regressions (Table 3): sepsis is highly significantly associated with this metabolic alteration.

Propofol intake

Altogether 144 patients (65.5%) received propofol ranging from 0.04 to 5.83 mg/ibw/h before their peak TG value. Patients with brain injury and multiple trauma received significantly higher doses of propofol (Table 1). A strong association between TG levels and propofol dose (mg/kg/h) and the propofol lipid vehicle was observed (r^2 = 0.28 and 0.26 respectively, p < 0.001). The median dose of propofol associated with hyperTG was 2.04

mg/kg/h. The magnitude of the TG increase (deltaTG) was influenced by the cumulated dose of propofol before the peak (r^2=0.038, p=0.0037), the propofol dose/kg/h (r^2= 0.061, p=0.0002), but less by number of days on propofol before the peak (r^2= 0.020, p =0.034) or lipid dose (r^2= 0.027, p= 0.013).

Total cholesterol and HDL-cholesterol levels were unaffected by the propofol dose.

Lipid intake

Fat from feeding (EN+PN) did not differ, while intravenous fat from propofol was proportional to the propofol dose and significantly higher in the hyperTG patients (Fig. 1). The correlation between lipid intake and TG levels was significant but less than that of propofol.

Discussion

The present study confirms that hyperTG is very common in critically ill patients, being observed in 45% of patients requiring at least 4 days of ICU treatment. It takes a few days to develop, 7 as a median. The propofol dose and associated lipid vehicle with infection were the factors showing the strongest association with this metabolic complication. The incidence of hyperTG varies widely in the literature, ranging from 18% to 38% (2, 39). These differences are attributable to the variability of the patient cohorts, the treatments and the definition of hyperTG, ranging from > 1.7 mmol/L to ≥ 5.65 mmol/L (2, 39). Indeed the proportion of patients in our cohort presenting values exceeding 5 mmol/L was only 4.5%. The observed changes in TG levels were not a unified process, but the conjunction of an infection and high dose propofol as shown in Fig. 2 was a frequent pattern. High dose propofol resulted in increased fat delivery. The association between the propofol dose (1% or 2%) and the TG concentrations has been previously investigated, but the time

relationship has been inconsistent. McLeod et al. (38) found a similar association in 30 ICU patients who received exogenous lipids only from propofol over 50 hours. HyperTG induced by propofol has mainly two possible causes: the most likely is the fat emulsion vehicle itself, and possibly but less likely the inhibition of the fatty acids metabolism in the mitochondria (36, 119, 120) caused by an uncoupling the oxidative phosphorylation and energy production (44). Some authors have reported that hyperTG was not directly associated with the total amount of infused lipids (23, 39) which is interesting as the propofol's LCT emulsion is identical to that used for PN (36, 121). Moreover, Theilen et al. (37) failed to demonstrate the superiority of a LCT/MCT propofol formulation (supposed to reduce the occurrence of hyperTG), suggesting that lipids associated with propofol were not responsible for the TG alterations. However, the prolonged administration of propofol, which amounted to 15.9% of the total fat delivery in our study, may require an adjustment of PN or EN to avoid overfeeding during propofol sedation (49). From a metabolic point of view it is important to be aware that a very common 200 mg/hour propofol sedation rate (i.e. 4800 mg of propofol/24h) results in the delivery of 24 g of fat with a 2% solution, and 48 g with a 1% solution. Importantly, as our ICU uses 2 different concentrations, there is a slight variation of the propofol related lipid intake, explaining the stronger correlation with propofol, directly followed by the lipid dose.

Parenteral lipid intake is known to exacerbate hyperTG during acute illness (2, 15). Guidelines for parenteral fat intake (11) were respected. Enteral fat is efficiently absorbed, and high doses might alter the lipid profile in case of long term EN (122) but no association with hyperTG was observed in our cohort. This is probably explained by the use in our hospital of MCT/LCT based EN solutions, reducing its impact on TG. Our data confirm that hyperTG does not occur when maximal nutritional lipid intakes are respected, the propofol remaining a specific determinant of hyperTG. Among lipids, MCTs containing emulsions

seem to be associated with less hyperTG (2, 103), although this remains controversial (92): as the number of patients on MCT-propofol was low we could not confirm such a benefit. Overfeeding by any route with glucose or/and fat is a common cause of hyperTG (99), which was not observed in our cohort where overfeeding was an exception. All patients were monitored daily to prevent overfeeding an the energy target was frequently verified by indirect calorimetry. Our CIS shows the cumulated glucose dose from both enteral and intravenous routes enabling thereby to avoid exceeding the maximal oxidation capacity of 5 mg/kg/hour (11) and the risk of de novo lipid synthesis(101).

The strong association of TG values with CRP confirms that the acute-phase response causes significant changes to the lipid metabolism (38). Infection was present in 75.8% of the patients at the time of hyperTG: the conjunction of an inflammatory response with an elevated propofol dose seems to increase the risk of developing hyperTG.

There was no increase in mortality with hyperTG, but with modest hyperTG (only 10 patients had values > 5 mmol/L) the impact on outcome is uncertain. Currently, clinical consequences of acute and transient hyperTG remain poorly known, although cases of acute pancreatitis, fatty liver, delayed awakening, retinal lipemia (2, 15, 23) and elevated mortality particularly in association with hypocholesterolemia (102) have been described. An increased risk of infection by disruption of the reticuloendothelial system (2, 103), coagulopathy (38), neurological disturbance or respiratory failure (2) have also been reported, none of which occurred in our patients.

Seventy patients (32%) were on statins: hyperTG was as frequent in these patients as in those without. They had received smaller doses of propofol, and importantly they suffered significantly fewer infectious episodes (p=0.0023). At a smaller scale these data are in line with the results of a recent case control study including 7’223 cases of pneumonia (out of 71’000 hospital admissions) which showed that the use of statins decreased pneumonia risk

and 30-day mortality (123). But the effects of statins on lipid metabolism are pleiotrophic, and they are not first intention treatment of a hyperTG: absence of impact on TG levels is therefore not surprising.

Limitations of the study

The principal limitation of this prospective non interventional study is the modest size of the cohort which limits the analysis of the risk factors (n=220, 45% hyperTG): the low number of patients suffering the predefined risk pathologies precludes drawing strong conclusions. However the small number of observations has to be weighted by the inclusion of very sick patients with a median stay of 10 days and 18.6% hospital mortality, and the very complete metabolic outwork available in the database. The high proportion of patients receiving the sedative drug propofol nevertheless enables analyzing the impact of this specific drug on the risk of developing hyperTG. With the presence of sepsis, it was the strongest determinant of hyperTG. The most likely explanation is that the other factors have a lesser impact on lipid metabolism in the critically ill.

Another limitation is the wide spectrum of pathologies present in the cohort, and presumably of their genetic characteristics: both modulate the metabolic responses to feeding and to sepsis. In absence of more information, this aspect cannot be explored.

Conclusion

HyperTG is frequent during critical illness affecting 45% of the present cohort: the TG values remained below 5 mmol/L in the majority of the patients. Although this alteration was not associated with any worsening of outcome, the variability of the response justifies a monitoring of the TG levels in case of propofol sedation: propofol was the external factor most strongly associated with hyperTG. Propofol may be a surrogate though, and this study

could not establish if it was the drug itself or the lipid vehicle that favoured hyperTG. The simultaneous presence of an infection reinforced the TG increase confirming the impact of the acute phase response on lipid metabolism. On the other hand moderate nutritional fat intakes (enteral or parenteral) do not cause this alteration. The TG levels of patients sedated with propofol should therefore be regularly monitored, probably 2-3 times weekly. Finally, the role of the propofol should be further investigated and clinical consequences of hyperTG remain to be established.

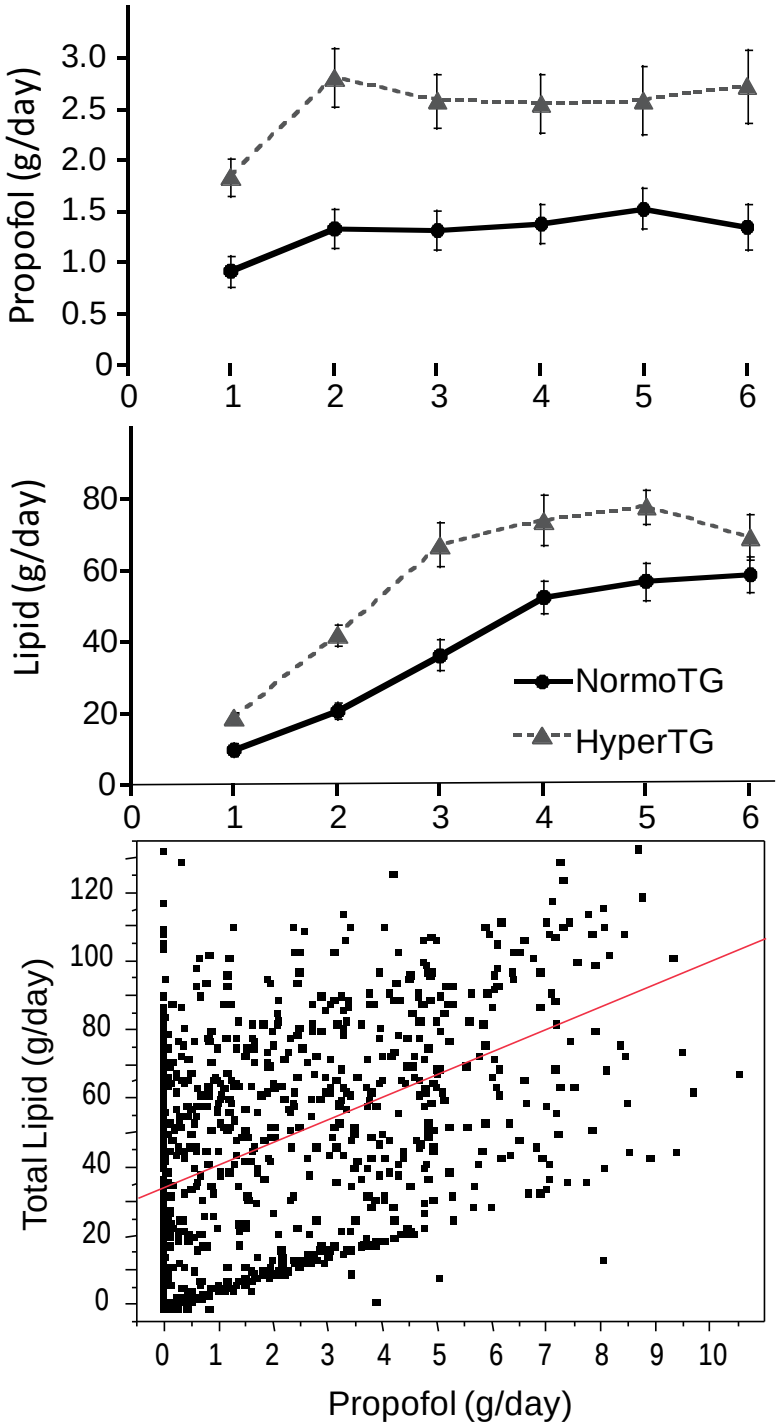

Fig. 1: Evolution of propofol and total lipid delivery during the first 6 days before the peak TG value which occurred as a median on day 7 in normo- and hyperTG patients. The lower box shows the significant relationship existing between the propofol dose/day and the lipid dose/day.

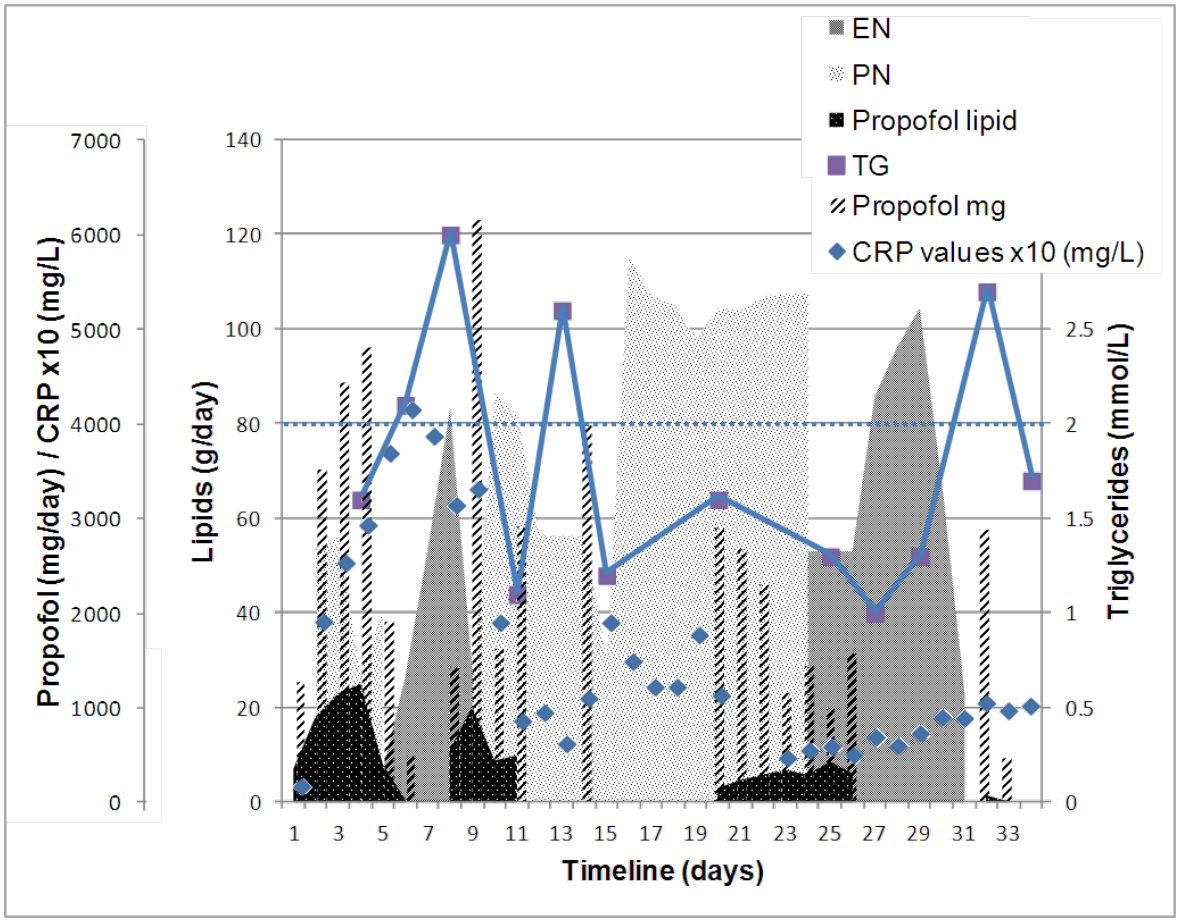

Fig. 2: Example of plasma triglyceride evolution with the cumulated daily dose of the different lipid types over time (EN = enteral nutrition, PN = parenteral nutrition).the total daily propofol dose (dash line = hyperTG reference). In this case events prior to day 8 (highest TG peak) were considered for analysis.

Table 1: Demographic and biological characteristics

Variable	All (n=220)		NormoTG (n=121)		HyperTG (n=99)		p value
Age (years)	62 [48 ; 73]		66 [57 ; 74]		57 [42.5 ; 66]		<0.001
BMI (kg/m^2)	25.3 [22.75 ; 28.7]		25 [21.675 ; 28.4]		25.8 [23.4 ; 29.4]		0.023
SAPS II	45 [37 ; 53]		47 [40 ; 55]		43 [35 ; 51]		0.023
Medical / surgical	37.7% / 62.3% (83/137)		38%/62% (46/75)		37.4%/61.6% (37/62)		NS
Gender M/F	70.9%/29.1%/ (156/64)		69.4%/30.6 % (84/37)		72.7%/27.3 % (72/27)		NS
Types of pathologies	N	propofol mg/kg/h	N	propofol mg/kg/h	N	propofol mg/kg/h	
Abdominal	40	0.44	19	0.27	21	0.56	
Cardiac	59	0.51	42 *	0.46	17	0.59	
Respiratory	44	0.91	24	0.45	20	1.59	
Trauma	25	1.67**	8	1.53	17 *	2.07	0.004
Brain Injury	13	3.91**	4	3.22	9 *	4.09	
Neurological	24	0.82	17	0.82	7	0.94	
Other	15	0.29	7	0.08	8	1.10	
Sepsis	124 (56.4%)		49 (40.5%)		75 (75.8%)		0.019
Lipid profile							
Peak Triglycerides (mmol/L)	1.9 [1.4 ; 2.9]		1.5 [1.1 ; 1.7]		3 [2.6 ; 3.9]		<0.001
Reference TG	1.2 [0.8 ; 1.7]		0.9 [0.7 ; 1.2]		1.7 [1.35 ; 2.3]		<0.001
Delta TG (ref-peak)	0.7 [0.4 ; 1.3]		0.5 [0.3 ; 0.6]		1.3 [0.9 ; 1.9]		<0.001
Time in ICU before peak	7 [4 ; 9]		7 [4 ; 9]		7 [4.8 ; 9]		NS
Time on propofol before peak	3 [1 ; 6]		2 [0 ; 5]		4 [2 ; 6]		0.025
HDL-Cholesterol (mmol/L)	0.6 [0.3 ; 0.9]		0.8 [0.5 ; 1.1]		0.4 [0.2 ; 0.7]		<0.05
Total Cholesterol (mmol/L)	3.5 [2.6 ; 4.2]		3.3 [2.5 ; 4]		3.7 [2.7 ; 4.7]		NS
Intakes							
Energy delivery (kcal/kg/day)	16.8 [11.4 ; 22.5]		15.4 [9.2 ; 22.5]		18.3 [13.3 ; 22.2]		NS
Total glucose (g/kg/day)	2.1 [1.4 ; 2.8]		2.1 [1.4 ; 2.8]		2.1 [1.6 ; 2.7]		NS
Total Fat (LCT+MCT) (g/kg/day)	0.6 [0.4 ; 0.8]		0.6 [0.3 ; 0.8]		0.7 [0.5 ; 0.9]		0.013

TPN Fat (LCT+MCT) (g/kg/day)	0 [0 ; 0.3]	0 [0 ; 0.3]	0 [0 ; 0.3]	NS
Enteral Fat (g/kg/day)	0.4 [0 ; 1]	0.4 [0 ; 1]	0.5 [0.1 ; 1.1]	0.049
Propofol (mg/kg/h)	1.4 [0.7 ; 2.2]	1.1 [0 ; 1.9]	1.8 [1 ; 3]	<0.001
Outcome				
Mechanical ventilation (days)	7.4 [4.6 ; 11.5]	6.6 [3.9 ; 9.7]	9.2 [6 ; 13.2]	0.021
Length of ICU stay (days)	10.4 [7.5 ; 15.5]	8.8 [6.7 ; 13.4]	13 [8.7 ; 17.4]	<0.001
ICU Mortality (%)	9.5 % (21)	9.9 % (12)	9.1 % (9)	NS
Hospital Mortality (%)	18.6 % (41)	20.7 % (25)	16.2 % (16)	NS

Results are expressed as median and [interquartile range] or as percentage and (number of subjects). BMI: body mass index; HDL: high density lipoprotein; LCT: long chain triglycerides; MCT: medium chain triglycerides. The weight used for calculations is the ideal body weight.
*: significant difference; ** p <0.0001

Table 2: Correlation between selected daily parameters and peak triglyceride concentration

Parameter Term	Pearson's coefficient (r^2)	Significance
Propofol (mg/kg/h)	0.28	<0.001
Lipids from Propofol (g/kg/d)	0.26	<0.001
CRP (mg/L)	0.19	0.004
Total lipid intake (g/kg/d)	0.14	0.024
Cumulative glucose intake (g/d)	0.12	NS
(g/kg/d)	0.11	NS
Cumulative energy intake (kcal/kg/d)	0.09	NS
LCT + MCT parenteral lipids (g/kg/d)	0.07	NS
Total of LCT intake (g/kg/d)	0.04	NS
LCT + MCT enteral lipids (g/kg/d)	0.04	NS
Insulin dose (UI/24h)	0.02	NS

LCT: long chain triglycerides; MCT: medium chain triglycerides; TPN: total parenteral nutrition.

Propofol dose is the mean dose per ideal body weight per day between admission and peak TG value.

Cumulative glucose and energy intakes: integration of intakes from admission

Table 3: Plasma Triglyceride value and propofol doses of the different diagnostic categories

	Triglyceridemia [mmol/L]	Median propofol dose [mg/kg/h]	All (n=220)	NormoTG Patients (n=121)	Odds ratio (95% CI)
Control group	1.6 [1.3 ; 2.3]	0.8 [0.2 ; 1.7]	73	50	0.4 (0.2-0.8)
Other groups at risk	1.4 [1.2 ; 1.6]	0.3 [0 ; 0.8]	11	10	0.1 (0-0.9)
Dyslipidemia	1.2 [1.1 ; 1.5]	0.6 [0.1 ; 0.9]	12	12	NA
Sepsis	2.4 [1.7 ; 3.4]*	0.9 [0.1 ; 2]	124	49	4.6 (2.5-8.2)

Results as median and [interquartile range]; * are significantly different from the control group ($p<0.001$). Other groups at risk are composed of diabetes mellitus, chronic renal failure and pancreatitis.

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CHAPITRE IV

Article III

Example of a pharmacoeconomic modelling in an ICU environment: The case of prefilled propofol syringes to reduce primary bacteraemia in critically ill patients.

J.-C. Devaud, PharmD [1, 2], P. Voirol, PhD [1,2], P. Jolliet, MD PhD [3], C. Pinget, PhD [4], J.-.B. Wasserfallen, MD PhD [4], A. Pannatier, PhD [1, 2], P. Eggimann, MD PhD [3]

Running title: Pharmacoeconomic evaluation of propofol syringe contamination

1. Service of Pharmacy, Lausanne University Hospital, Switzerland.

2. School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, Switzerland.

3. Service of Adult Intensive Care Medicine & Burns, Lausanne University Hospital, Switzerland.

4. Health Technology Assessment Unit, Medical Directorate, Lausanne University Hospital, Switzerland

Résumé:

Introduction : Les stratégies permettant de minimiser la marge d'erreur ou qui améliorent les soins des patients tout en réduisant les coûts et les risques sont en augmentation d'intérêt pour les responsables de soins intensifs. De prime abord, les seringues de propofol préparées manuellement paraissent bien moins coûteuses que les seringues prêtes à l'emploi et pourraient par conséquent être largement privilégiées dans les unités de soins intensifs. L'objectif de ce travail a été d'identifier et de comparer les probabilités et les coûts des infections entre les seringues prêtes à l'emploi et préparées de propofol au lit du patient.

Méthodes : Les taux d'infection du sang rapportés à l'utilisation des deux types de préparation ont été calculés sur la base des données relevées dans d'autres études. Le résultat d'une durée additionnelle de séjour provoquée par une infection du sang a été estimé par un modèle mathématique. Le coût de chaque stratégie a été estimé par des méthodes de coûts détaillés.

Résultats : Le risque de développer une infection du sang par une préparation contaminée contenant du propofol est de 22.6% (95% IC, 0-74.4%). Les seringues prêtes à l'emploi et celles préparées manuellement avaient des probabilités d'infection de 0.0014 (95 % IC, 0.0009–0.0038) et 0.0118 (95 % IC, 0.0056–0.0181), respectivement. Les durées de séjour additionnelles aux soins intensifs dus à une infection du sang rapportée allaient de 5.3 à 11.4 jours. Comparées aux seringues préparées manuellement, les seringues de propofol prêtes à l'emploi ont diminué les coûts des séquences de sédation de $431($188–$773) à $149 ($111–$306).

Conclusion : Malgré un coût plus élevé à l'achat, les seringues prêtes à l'emploi de propofol est une stratégie potentiellement coût efficace en comparaison des

seringues préparées manuellement. Notre étude suggère un impact potentiel sur l'économie d'une unité de soins intensifs et sur le devenir des patients.

Abstract

Objective: Strategies that minimums the margin of error or improves patient care, as well as reducing costs and risks are of increasing significance to intensive care unit (ICU) managers. In the first place, manually prepared propofol syringes appear much less expensive than prefilled syringes and, therefore, could be widely preferred in ICUs. We aimed to identify and compare the probability and cost of infection between prefilled and manually filled propofol syringes. *Design:* Rates of propofol-related blood stream infection (BSI) from using the two preparation types were computed on the basis of data from previous studies. The resulting additional length of stay (LOS) in the ICU due to BSI with was estimated by a disability model. The cost of each strategy was estimated by microcosting methods.

Setting: 32-bed adult mixed ICU in a tertiary hospital in Switzerland.

Interventions: None.

Measurements and Main results: The risk of developing BSIs from contaminated propofol preparations was 22.60 % (95 % CI, 0–74.36 %). Prefilled and manually filled syringes had infection probabilities of 0.0014 (95 % CI, 0.0009–0.0038) and 0.0118 (95 % CI, 0.0056–0.0181), respectively. Additional LOS in the ICU due to BSIs ranged from 5.3 to 11.4 days. Compared to manually filled propofol syringes, prefilled syringes decreased the cost per sedation procedure from $431 ($188–$773) to $149 ($111–$306).

Conclusions: Despite a higher ex-factory cost, prefilled propofol syringes in place of manually prepared syringes is a potentially cost-effective strategy. Our study indicates a potential impact of using prefilled syringes on ICU economic and clinical outcomes.

Introduction

Today a large proportion of the hospital budget is taken by intensive care unit (ICU) and has developed to become an essential part of all modern hospitals. The fundamental question is how is, the ICU with its high cost and high safety incident rate, best to organize the available health technology and human resources to fulfil the needs of critical care interventions. ICU managers are increasingly faced with difficult financial decisions regarding how best to allocate growing limited funds without reducing standards of care or negatively impacting on patient outcomes. Any action that minimums the margin of error or improves patient care, as well as reducing costs and litigation risks is of increasing significance to ICU managers. In the search for solutions to this funding dilemma, pharmacoeconomics methods to reduce ICU costs have been proposed. Recently we assessed the evolution of ICU drug prescription both in quantities and costs, by type of prescriber (124). This led us to have a prospective follow-up of the costs in our ICU and to have a systematic screening of the possible savings. One cost driver are bloodstream infections (BSIs) and account for approximately 5–15 % of all nosocomial infections and are associated with increased hospital length of stay (LOS) and costs (50, 51). One possible strategy to reduce BSIs is to use prefilled syringes instead of manually filled syringes in order to reduce primary bloodstream infections. These contaminations are defined as a microbiologically bloodstream infection without any documented source (51). Critically ill patients are at particularly high risk of primary bacteraemia because they are frequently catheterised and given drugs formulated in lipid emulsion (51-56). Primary bacteraemia in the presence of an indwelling catheter is considered to be catheter-related in 90 % of cases (125).

Numerous outbreaks of nosocomial BSI linked to the contamination of drug solutions have been reported (55, 56, 60, 65), and such contamination is well-recognised as an important source of BSI (51). This risk appears to be increased with the use of propofol (52) because of its lipid emulsion formulation, its storage temperature, and nursing practice (3, 56, 61, 66). As continuous propofol infusions are used to provide sedation in critically ill patients, this drug appears to be a good challenger to reduce costs in ICU. In a literature review and meta-analysis (126) of 4,036 examinations of multiple-dose vials from 12 different studies, the average contamination rate was only 0.6 %. More recently, Buckley et al. (127) reported a contamination rate of 1 % for single-dose vials and up to 5 % for multiple-dose vials.

In accordance with the local nurse practices, the uncapped rubber stopper of the propofol vials (50 mL) is sometimes disinfected with isopropyl alcohol (70%) before filling the syringes. Furthermore, when a syringe was empty it was replaced with a new, freshly prepared one. Although low, a risk of BSI secondary to contamination of manually filled propofol syringes has been reported among patients in the intensive care unit (ICU) (53). In this context, the risk of extrinsic contamination of preservative-free propofol solutions is much less likely with the use of “prefilled” (or prefilled) propofol syringes that are manufactured according to strict industry standards (52, 53, 55, 60, 64, 66, 128). Studies of contamination of prefilled syringes are scarce, but the incidence of contamination of these syringes has generally been reported to be less than 1 % (71, 73, 129).

In addition to incorrect handling of propofol preparations, infusion time sometimes extends beyond the time recommended by the manufacturer (53), thereby further increasing the risk of bacteraemia if contamination occurs.

The overall aim of our study was to present a pharmacoeconomic model to determine whether the additional cost associated with using prefilled syringes would offset the costs stemming from possible contamination in a clinical setting. To achieve this aim, we first estimated and compared the probabilities of contamination between manually filled and manufacturer-provided prefilled propofol syringes. We then explored the likely costs associated with contamination of each type of propofol syringe.

Material and methods

Setting

Local observations and costs were based on data extracted from the 2012 Case-Mix Database of a 32-bed adult mixed ICU in a tertiary hospital. The ICU admits about 2,200 patients per year, totalling approximately 11,000 patient-days. Nurses perform the sedation procedures and achieve target sedation levels, which are specified in a sedation protocol that is based on published recommendations (130, 131).

Perspective

The economic analysis was performed from a hospital perspective. Only direct medical costs (i.e., patient monitoring devices, medical therapy, concomitant medications, hospitalisation days including salaries, and duration of therapy, cost of diagnosis) for treating nosocomial BSIs were included. Other individual medical costs (i.e., laboratory tests, radiographic imaging studies, drugs, surgical procedures, etc.) related to other underlying diseases were not taken into account because they are not a consequence of contaminated syringes.

Literature search

We conducted a MEDLINE-based literature search for incidences of contamination of manually filled and prefilled propofol syringes over the period from 1993 to 2012, using “drug contamination” and “incidence” as medical subheading (MeSH) terms. Complementary searches were conducted using the MeSH terms “propofol” and “contamination”. Reference lists of all selected articles were screened to ensure completeness of information. We selected articles according to the following criteria:

1) The study was published in English, French, or German.
2) The study evaluated the incidence of contamination of prefilled and/or manually filled propofol syringes.
3) The article discussed the concordance between bacteria identified in the syringe and bacteria in the patient’s blood.
4) The methodology used to prepare propofol infusions (i.e., prefilled or manually filled syringes) was similar to practices in our ICU.

Cost of propofol-related BSI

Cost of propofol preparation

Three propofol formations are used at our hospital: two 2 % solutions for continuous sedation (a 50-mL prefilled syringe, Disoprivan, Astra Zeneca, Zug, Switzerland, and a 50-mL vial, Propofol-Lipuro, B. Braun Medical AG, Sempach, Switzerland) and a 1 % solution for short procedures (10, 20, and 50 mL Propofol-Lipuro, B. Braun Medical AG). The ex-factory cost (i.e., without the margin) of each propofol formulation was used in the cost analysis.

The cost per injection of propofol was estimated by the microcosting analysis of data obtained from a time-and-motion study of randomly chosen propofol preparation procedures. The time-and-motion study was developed by Frederick Winslow Taylor in 1911 to determine the minimum amount of time needed to complete each stage of a task. The results of such a study can be used to improve productivity. For this time-and-motion study, we measured the time needed, the number of nurses involved, and the material used per propofol preparation procedure.

Cost of pathogen diagnosis

All costs were obtained from the cost-accounting system at our hospital.

Cost of treatment

Microcosting analysis of propofol-related infections caused by pathogen species described in the literature was performed. Based on the median ($575) and range ($146–$3229) provided by Schwebel et al. (57), we assumed that the treatment of a catheter-related infection was similar to the treatment of a propofol-related BSI.

Cost of additional LOS

Additional LOS in the ICU due to propofol-related BSI was estimated by the multistate disability model (132, 133) of the values found in the litterature, which averages the difference in LOS at each day between infected and noninfected patients. The method also accounts for death and discharge. The additional LOS was multiplied by our direct cost per ICU day (excluding costs related to other underlying diseases, as described above), which was derived from the cost-accounting system for medical and surgical ICUs. The total cost of one propofol-

related infection was estimated as the sum of direct costs of propofol preparation, pathogen diagnosis, and treatment plus the cost of the additional LOS.

Main assumptions used for the cost analysis

Although most costs were derived from direct observations, we made a few assumptions:

1) The cost of propofol-related infection was independent of the outcome (survival or death).
2) Contaminated propofol syringes that did not result in BSI had no additional costs or adverse outcome.
3) Costs measured in Swiss Francs (CHF) were converted to US Dollars (USD) with the 2013 exchange rate posted on a foreign currency exchange site (http://www.oanda.com) (1
USD = 0.9 CHF).

Pharmacoeconomic model structure

We developed a pharmacoeconomic model to determine the expected cost of an infection per unit of propofol, based on the probabilities of infection from prefilled and manually filled syringes. This model was based on data obtained from the literature according to a strict literature search protocol. A decision tree was developed with TreeAge software (TreeAge Software Inc., Williamstown, MA, USA) and was applied to the costs and outcome comparison between prefilled and manually filled propofol syringes. The model included four possible adverse event

outcomes, depending on whether the propofol-containing syringe was prefilled or manually prepared, as shown in Fig. 1.

Model inputs

We used data extracted from our clinical information system (Metavision, iMDSoft, Tel Aviv, Israel). These data included the frequency of use of manually filled and prefilled propofol syringes, based on the duration of use and the dose actually administered to patients throughout the year 2012. Incidence of contamination or potential transmission of contaminated bacteria to a patient was derived primarily from study findings. The probability of infection was assumed to be the same, regardless of the dose administered. Probabilities of infection obtained from the articles were used for the model input.

Sensitivity analyses

Different cost and probability scenarios, produced by modifying the assumptions and the values of several key variables, were analysed to assess the robustness of the model's conclusion. For any variable, the highest and lowest values were used to replace the baseline value. When the substituted value changed the model's conclusion, the baseline value was replaced with additional values in the variable's range. This process was repeated until we determined the exact value (or range of values) of the variable that changed the conclusion.

Because acquisition prices are negotiated between the hospital and pharmaceutical industry, the impact of modifying the prices of vials and prefilled syringes was evaluated. Sensitivity analysis was used to evaluate the impact of an additional LOS in the ICU related to infection, by using the change in LOS (clos) function in the empirical transition matrix package of R programming software (R

Foundation, version 2.15.0). Uncertainty analysis with a Monte Carlo simulation (1000 runs) was performed in the TreeAge Pro software package (version 2011), to investigate the likelihood that there was an economic advantage of using prefilled instead of manually filled propofol syringes. Obtaining accurate results from a probabilistic sensitivity analysis typically requires 600 to more than 1000 model runs (134, 135).

Results

In our ICU, the total propofol cost was $326,013 for the study year (8 % of the total ICU drug budget). The distribution of costs between prefilled and manually filled syringes was $317,911 (for 12,593 continuous sedations and 1,414 bolus sedations) and $8,102 (for 836 continuous sedations and 154 bolus sedations), respectively.

Literature search

Using MeSH terms, 13 articles were screened, of which 8 studies (61.5 %) were eligible for this study based on similarity to our ICU practice. An additional 3 articles (23.1 %) were excluded due to lack of discussion regarding the concordance between the bacteria identified in the syringe and in the patient's blood. Probabilities of infection derived from the 5 remaining articles were used for the model input. The incidence of contamination of propofol syringes (regardless of type) varied between 0 % and 11 % among published articles (52-55, 64-68, 129). Contamination rates of manually filled propofol syringes were generally higher and more variable (1.6–5.9 %) and compared to contamination rates of prefilled propofol syringes (0–1.9 %) (52, 53, 55, 66, 129).

Cost of propofol-related BSI

Cost of propofol preparation

The workforce cost calculated from the time-motion study data was, itself, not a representative cost of propofol preparation; therefore, it was included directly in the total cost for propofol preparation. Ex-factory costs of 50-mL prefilled syringes of 1 % and 2 % propofol were $27.60 and $45.10, respectively. Ex-factory costs of 50-mL vials of 1 % and 2 % propofol were $15.00 and $24.80, respectively. According to our practice guidelines, the prefilled syringes and vials were used only once.

Cost of pathogen diagnosis

According to the local pricing the cost of diagnosing the pathogen included the cost of blood cultures ($66.70) and the cost of antibiotic susceptibility testing when the culture result was positive ($21.80).

Cost of treatment

The calculated median direct cost of treating a propofol-related infection was $723.60 ($152.80–$3,370.00).

Cost of additional LOS

The direct cost per ICU day estimated by our accounts department in our hospital was $2,379.40. Additional LOS for an infection in hospitals were reported to range from 5.3 [3.7; 6.9] to 11.4 [4.1;18.6] days from the literature (57, 132, 133), which translated into a median cost of $27,125.2 ($9,755.5–$44,256). Based on studies (53, 60) that identified the bacteria responsible for propofol syringe-related infections by genotyping, the estimated mean and median risks of a patient developing an infection from a contaminated propofol preparation were 22.60 % (95 % CI, 0–74.4 %) and 27.0 %, respectively. Taking the sum of the individual costs reported above, the total cost of BSI from a contaminated prefilled propofol syringe ($27,982.4) is very similar to that of BSI from a contaminated manually-filled syringe ($27,962.1). However, these total costs do not take into account the difference in the probability of causing infection between prefilled and manually-filled syringes

Pharmacoeconomic results

When the probabilities of infection from prefilled and manually filled syringes were included in our pharmacoeconomic model, cost-analysis revealed that using prefilled instead of manually filled syringes decreased the expected cost of infection per unit of propofol from $431 ($188–$773) to $149 ($111–$306), p = 0.001. This change translated into a cost savings of $282 per sedation procedure (Table 2).

Sensitivity analyses

Results of the sensitivity analyses are shown in Fig. 2. Main cost drivers were the costs induced by the probability of infection with prefilled syringes and the additional LOS. The cost driver most sensitive to variation was the probability of infection with prefilled syringes, whereas the cost driver least sensitive to variation was cost associated with infection.

Table 1 reports the baseline variable values that we obtained from the literature or calculated from our own data, and the value ranges over which these variables were analysed by the Monte Carlo simulation.

Discussion

Our study indicates a potential impact of using prefilled syringes on ICU economic outcomes.

The theoretical increased efficiency associated with the prefilled syringes and the reduced infection rates on such units have often been promoted (53, 66, 71) as likely to be associated with reduced costs (51, 136). In an early systematic review of the literature, only two studies were identified that had conducted economic analyses and they all concerned infection rate. The authors concluded that there was a lower infection rate with the use of prefilled syringes rather than manually filled syringes which showed a reduction of total parenteral injection costs (51, 136). Our findings support this conclusion and revealed that, compared to preparing a propofol syringe at the bedside, using a prefilled propofol syringe during a sedation procedure could save $282 per procedure. Implementing prefilled syringes was a cost-saving strategy, despite the reported propofol-related infection rate of 0.38 % (71, 73, 129). This infection rate was lower than that

associated with using manually filled propofol syringes (0.58 %) (52-55, 59, 60, 65-67, 71, 73, 129).

Assessing cost differences occurring as a result of introducing prefilled syringes can be difficult, with the existing literature using the infection rates data, which does not factor in the reduced acuity and cost of treating BSIs and related additional LOS in the ICU. The median cost of treating propofol-related BSIs determined in our study is similar to the cost of preventing catheter-related intravascular infections reported in other studies (57, 125). The cost savings achieved by shifting patients from manually prepared syringes to prefilled syringes of propofol need to be calculated as the total cost of ICU care and the variability associated with all parameters in order to give enough inputs to the sensitivity analysis.

Interestingly, the total costs among all cases of propofol-related BSI that we studied shared a common pattern related to the main cost driver. Avoiding an additional LOS in the hospital due to a BSI always leads to a cost savings of $100–$200 (57, 125, 133, 136). In our analysis, the median cost of an additional LOS due to propofol-related BSI was quite high ($26,878). This finding indicates that every measure should be taken to avoid BSIs in a clinical ward. Although the exact costs of nosocomial BSI vary in the literature, published values (137) range from $6,720 to $33,250. Our total cost of a propofol-related BSI, including the costs of propofol preparation, diagnosis, treatment, and additional LOS due to infection, is within this range.

It is interesting to note that our findings obtained by using mathematical modeling are similar to those obtained by using a matched case-control design. As hospitals

are directly responsible for the funding of infection control and quality improvement programs, along with nursing and sedation therapy staffing, and are therefore in the best position to directly influence infection rates.

Several mechanisms may increase the risk of propofol-related BSI in ICU patients. First, propofol impairs monocyte and neutrophil functions (138) and decreases bacterial clearance (139). Second, long-term propofol infusion has been associated with increased serum lipid levels (2, 140), which lead to progressive lipid accumulation that, in turn, impairs mitochondrial oxygen uptake in immune cells (44, 141). Third, propofol preparations contain omega-6 proinflammatory fatty acids, which may contribute to the increased risk of infection (142).

Our study has several limitations. The risks of real contamination of propofol solutions and subsequent BSI are mostly speculative. A true risk determination would require systematic culturing of blood specimens and swabs of propofol solutions suspected of contamination. Such analysis has never been done (55, 66). We did not explore the benefit of prefilled propofol vials that can be used in volumetric infusion pumps. This analysis was not done because our sedation protocol requires the use of the more precise syringe pumps, and because it was not an option to switch from syringe pumps to volumetric infusion pumps in our setting. In addition, the severity of infection was not taken into account. The inclusion of additional costs associated with treatment of septic shock in our analysis might have resulted in a further increase in calculated cost-effectiveness of the prefilled syringe.

Conclusions

Bacterial transmission to patients during injection of contaminated medication is a well-recognised cause of bacteraemia. Our study supports the safety and value of prefilled medication syringes in a financially stressed health care setting. Moreover, our findings strongly suggest a pharmacoeconomic benefit associated with the use of prefilled propofol syringes in place of manually filled syringes. However, this benefit is clearly dependent on the propofol price, which may vary widely over time and in different regions. Hence, the extra cost of prefilled propofol syringes might be higher than the potential savings associated with them. Our findings support previous evidence of reduced cost from using prefilled medication syringes. Further studies are needed to confirm the cost-effectiveness of prefilled syringes in critical care settings.

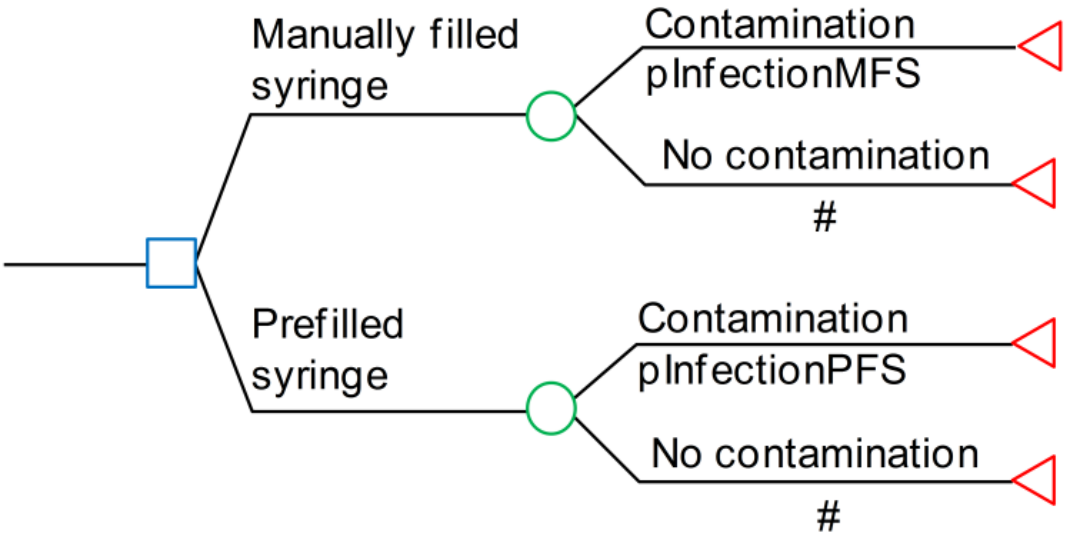

Fig. 1 Decision tree. *pInfectionMFS* probability of infection by using a manually filled syringe, *pInfectionPFS* probability of infection from using a prefilled syringe, # probability of no infection

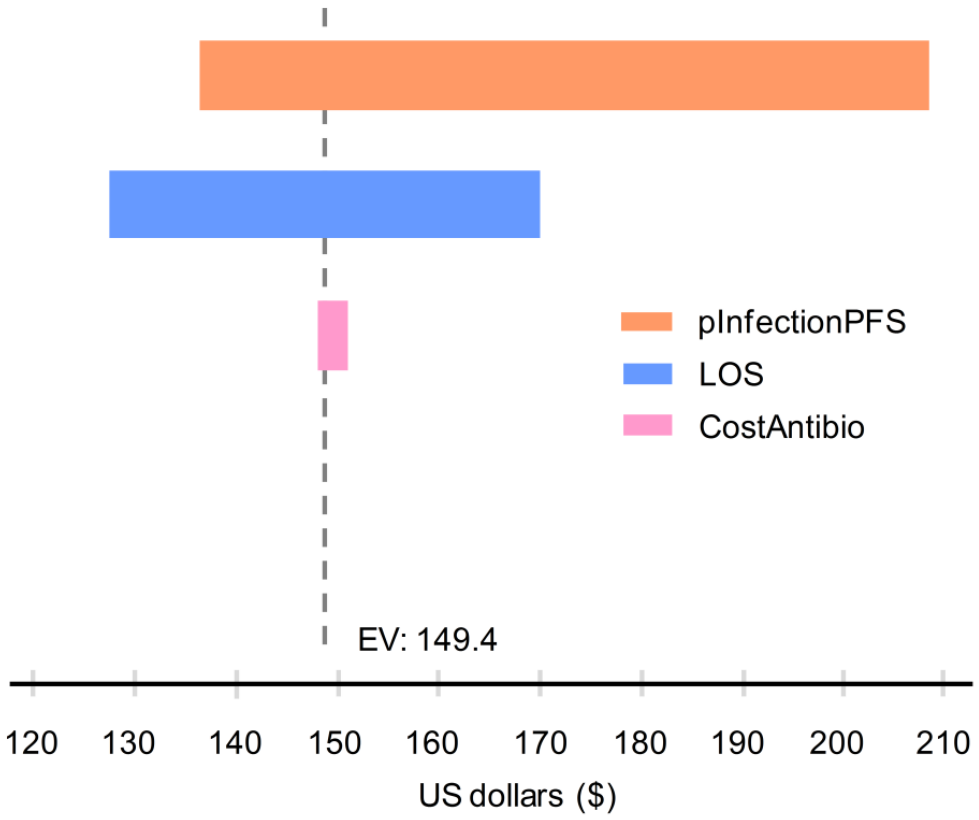

Fig. 2 Tornado diagram of one-way sensitivity analysis of cost-drivers. *PFS* prefilled syringes. Dollar amounts indicate the incremental cost per quality-adjusted life year. Coloured bars span between the lower and upper limits of the cost range for each respective variable. The single expected value (EV) is calculated at all upstream nodes and combines weighted average generated by an overall expected value for each strategy. EV of each scenario, identifies the decision maker's optimal strategy and enables testing and analysis of the recommendation.

Table 1 Ranges of variable values used in sensitivity analysis

Variable	Base value	Range of values	
		Low	High
Prefilled propofol[a] (probability)	0.0014	0.0009[a]	0.0038[a]
Prepared syringes[a] (probability)	0.0118	0.0056[a]	0.0181[a]
Antibiotic costs[b] ($)	723.60	152.80	3370
LOS costs[b] ($)	26,878	9,755.80	44,258.40

[a] Confidence interval calculated using bootstrap resampling of 1000 samples

[b] Data calculated from additional LOS and one ICU day cost

Table 2 Total and expected costs of infection from using prefilled and prepared propofol syringes

Decision tree branch	Cost of propofol preparation[a]	Cost of pathogen diagnosis[b]	Cost of treatment[b]	Cost of additional LOS due to infection			Total cost of infection[c]	Probability of infection	Expected cost of infection[c,d]
				per day	# of days	total			
Prefilled syringe / syringe pump + infection	45.1	88.5	723.6	2,379.4	11.4	27,125.2	27,982.4	0.0014	149.4 (111.2–306.3) [e]
Prefilled syringe / syringe pump + no infection	45.1	66.7	—	—	—	—	111.8	0.9986	
Prepared syringe / syringe pump + infection	24.8	88.5	723.6	2,379.4	11.4	27,125.2	27,962.1	0.0118	431.3 (188.2–773.2) [e]
Prepared syringe / syringe pump + no infection	24.8	66.7	—	—	—	—	91.6	0.9882	

All amounts expressed in US dollars ($)
[a] Per unit
[b] Per BSI
[c] Per infusion of propofol (sedation procedure)
[d] Cost based on probability of infection
[e] Ranges obtained from a Monte Carlo simulation of 1000 samples and 1000 trials

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CHAPITRE V

Conclusions et perspectives

8. Conclusion

Dans ce travail, nous avons pu démontrer que malgré un apport modeste de lipides, certains facteurs cliniques et l'apport de propofol semblent modifier la triglycéridémie. Toutefois, il n'est pas exclu que d'autres paramètres étant apparus comme non-significatifs puissent également jouer un rôle sur la triglycéridémie.

Il est également vraisemblable que l'apport de propofol en tant que principe actif ait un effet sur le métabolisme des acides gras. La quantité de propofol administré en continu modifie la triglycéridémie et pourrait contribuer à augmenter le risque de développement d'une hypertriglycéridémie.

Pour finir, il est important d'éviter toute contamination d'une émulsion lipidique utilisée dans les soins intensifs afin d'en éviter les importants coûts potentiels associés à une infection.

Ces différents travaux démontrent qu'il est nécessaire de choisir avec soin les émulsions lipidiques utilisées dans les soins intensifs en vue d'améliorer la qualité des soins prodigués aux patients et d'en limiter les aspects néfastes liés à leur utilisation.

9. Perspectives

La modification du profil lipidique et du profil des lipoprotéines semble dépendre de la phase aiguë présentée par un patient de soins intensifs dont le facteur causal peut être une blessure, un sepsis, la phase inflammatoire, etc.(143). Ces altérations pourraient augmenter la disponibilité de certains lipides spécifiques aux tissus endommagés et au système immunitaire. Le changement de composition observé dans les LDL et HDL pourrait avoir d'importantes conséquences au niveau de la paroi vasculaire en perturbant les propriétés de la balance pro- et anti-athérogénique ainsi que pro- et anti-inflammatoire.

Sur le plan du profil lipidique, une étude rapporte que la composition en triglycérides a une influence majeure sur le catabolisme des pseudochylomicrons (144). La clairance des oméga-6, qui composent majoritairement les nutritions actuelles, semble dépendre de la lipoprotéine lipase, de l'apolipoprotéine E, du récepteur de la lipoprotéine de basse densité et des voies sensibles à la lactoferrine tandis que la clairance des oméga-3 semble s'appuyer sur les lipoprotéines lipases dans une mesure très limitée et semble également être indépendante des autres voies. Les différences observées dans le catabolisme pourraient être le reflet direct des propriétés physico-chimiques intrinsèques des triglycérides.

Le mécanisme de clairance des oméga-3 doit encore être élucidé. Une étude chez la souris (20), rapporte que l'adjonction d'un faible pourcentage d'oméga-3 à une émulsion de LCT/MCT modifie le mécanisme de clairance des particules ainsi que l'absorption par les tissus. Une observation clinique (31) a également rapporté l'effet bénéfique de la perfusion d'oméga-3 pour le traitement d'une hypertriglycéridémie et la normalisation de la fonction hépatique. Concernant l'effet des oméga-3, une étude récente (145) rapporte que leur administration à raison de 0.2g/kg immédiatement avant l'injection de lipopolysaccharides, composants essentiels de la paroi des bactéries à Gram négatif, diminue la réponse inflammatoire provoquée par l'endotoxine. Une autre étude (101) a rapporté que les oméga-3 étaient bien tolérés et qu'une diminution des besoins en énergie était observée par le biais d'une régulation de l'homéostasie du glucose. Une revue récente (146) a rapporté que les connaissances actuelles suggèrent que les oméga-3 réduisent la mortalité, les infections secondaires et la durée de séjour chez les patients ayant présenté un sepsis, une réponse inflammatoire

systémique et/ou un syndrome de détresse respiratoire aiguë. Néanmoins, pour supporter les conclusions des études actuelles, il faudrait effectuer d'autres études randomisées contrôlées prospectives multicentriques avec des doses administrées en oméga-3 prédéterminées et des critères d'alimentation parentérale bien codifiés avec un collectif large et bien défini. Notons également que le développement actuel concernant les nutritions parentérales touche essentiellement les lipides. Il sera intéressant dans les années à venir de suivre l'impact réel de ces derniers sur la clinique et le devenir des patients de soins intensifs.

La pharmacoéconomie occupe une place croissante dans la rationalisation des décisions de santé hospitalière et des choix thérapeutiques. Les notions de bénéfice, d'efficacité, d'efficience et d'utilité doivent être clairement distinguées entre elles. Cependant, les méthodologies mises en œuvre doivent être mieux définies, pour permettre aux acteurs du domaine de se les approprier. La décomposition des coûts hospitaliers conduit à séparer les coûts directs (médicaux ou non médicaux), indirects ou intangibles ; les coûts fixes et les coûts variables. Le coût des effets indésirables, de la surveillance biologique, de l'administration du médicament et des échecs thérapeutiques doit être également pris en compte. L'analyse économique comprend la mesure la plus exhaustive possible de l'ensemble des coûts liés à l'utilisation des systèmes que l'on compare. Ici, les coûts retenus comportent classiquement les coûts des infections associés au type de dispositif d'administration du propofol.
Ces coûts sont reliés à des données d'efficacité clinique telles que documentées dans les évaluations cliniques appliquées à l'infection: probabilité d'infection, durée de séjour additionnelle, etc. Ainsi l'étude pharmacoéconomique est

totalement clinico-dépendante. La qualité et la robustesse des données présentées sont ainsi liées à la qualité des évaluations cliniques. Si les efficacités des prises en charge sont jugées comparables, seuls seront pris en compte leurs coûts dans le cadre d'analyses de type minimisation de coût. Pour des systèmes innovants (et coûteux), à l'efficacité supérieure attendue, l'analyse pharmacoéconomique comparera coût et efficacité des deux options de traitement. Le profil coût/efficacité des stratégies pourra lui-même être replacé dans la perspective d'autres interventions de santé. Il permettra ainsi aux praticiens d'éclairer leur processus décisionnel. Pour le médecin, le critère pharmaco-économique principal reste le rapport coût/efficacité, et non le coût d'acquisition des produits.

Ainsi la pharmacoéconomie, qui se trouve être une discipline jeune, cherche à se faire connaître et à être mieux comprise. Elle intéresse les décideurs, car son champ d'application est vaste et prend en compte tous les acteurs de santé. Dans le contexte des soins intensifs, toutes les stratégies qui pourraient diminuer la durée de séjour pourrait devenir coût-efficace. Cette constatation offre beaucoup de possibilités de recherche dans la perspective d'obtenir un système de santé toujours plus coût efficace.

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ANNEXES

Annexe I : Protocole NUTSIA

Le projet NUTSIA a pour objectif prioritaire d'améliorer la prise en charge nutritionnelle des patients en renforçant la structure d'accompagnement des équipes soignantes dans ce domaine et en mettant à leur disposition des outils de contrôles adaptés à leurs besoins. Plus en détail, ce protocole amène :

- un renforcement de la formation continue des équipes soignantes (médecins et infirmières) dans le domaine de la nutrition,
- un accès facile, informatisé, à une documentation de référence aussi synthétique et simple que possible,
- la mise en place d'une évaluation nutritionnelle systématique des patients suivie d'un contrôle,
- la transmission des informations à l'Unité de nutrition clinique lors du transfert de patients nécessitant une prise en charge nutritionnelle,
- un renforcement de l'encadrement avec la définition des rôles de chaque professionnel des soins intensifs dans la prise en charge nutritionnelle des patients et la désignation de personnes de référence dans ce domaine.

Les 3 pages suivantes ne présentent qu'une partie de la totalité du protocole NUTSIA.

Ici, la première partie du document explique comment dépister les patients à risque de dénutrition dès le premier jour par le calcul du score de risque nutritionnel (NRS) basé sur l'IMC, la perte de poids, la prise alimentaire, le niveau de stress et l'âge. La seconde partie donne des informations sur le choix du support nutritionnel et la dernière partie est un recueil des bilans métaboliques à effectuer lors de nutrition artificielle.

Service de médecine intensive
adulte et Centre des brûlés

Procédure

Evaluation nutritionnelle et choix du type d'assistance

NUTSIA : Nutrition Soins Intensifs Adultes

L. Soguel, M. Abando, Dr. M. Berger, S. Bouvry, C. Braichotte, D. Brunner, E. Foucault, P. François, Dr. M. Godio, S. Richard, A. Schmid, Dr. P. Turini
Révision : M. Charrière, Prof M. Berger

Validé par le CoPil : Prof. M.-D. Schaller, Prof. R. Chioléro, P. Cosse, P. Maravic, Prof. M. Roulet, Dr. J.-B. Wasserfallen 28.11.05
Version 2 : Dir Elargie SMIA 09.04.09 / **Version 3** : Dir Elargie SMIA 3.11.11

1. A. Evaluation nutritionnelle (score NRS-2002)

But : dépistage des **patients pour lesquels une assistance nutritionnelle est requise (NRS ≥ 4** avec ≥ 1 point dans l'item de détérioration de l'état nutritionnel) **ou à envisager.** Permet d'évaluer le degré de risque nutritionnel. (Niveau d'évidence A pour patients hospitalisés et chirurgicaux)

Calcul le jour qui suit l'admission du patient **(J1)** par l'équipe infirmière (consulté par médecin)

Calcul du score NRS-2002 : Nutritional Risk Screening 2002 (Kondrup et al 2003)

A. Détérioration de l'état nutritionnel (0 à 3 points)

Choisir parmi ces 3 facteurs celui qui vaut le plus de points (max. 3 points, min. 0 point)

BMI

> 20	0 point
18,5 à 20	2 points
< 18,5	3 points

Perte de poids % perte de poids = (poids antérieur - poids actuel) x 100 / poids habituel

< 5% en 3 mois	0 point
≥ 5% en 3 mois	1 point
≥ 5% en 2 mois	2 points
≥ 5% en 1 mois	3 points

Apports alimentaires durant la dernière semaine % des repas usuels censés couvrir des besoins nutritionnels

A mangé > 75 %	0 point
A mangé 50 à 75%	1 point
A mangé 25 à 50%	2 points
A mangé 0 à 25%	3 points

B. Sévérité de la maladie (stress) (2 à 3 points)

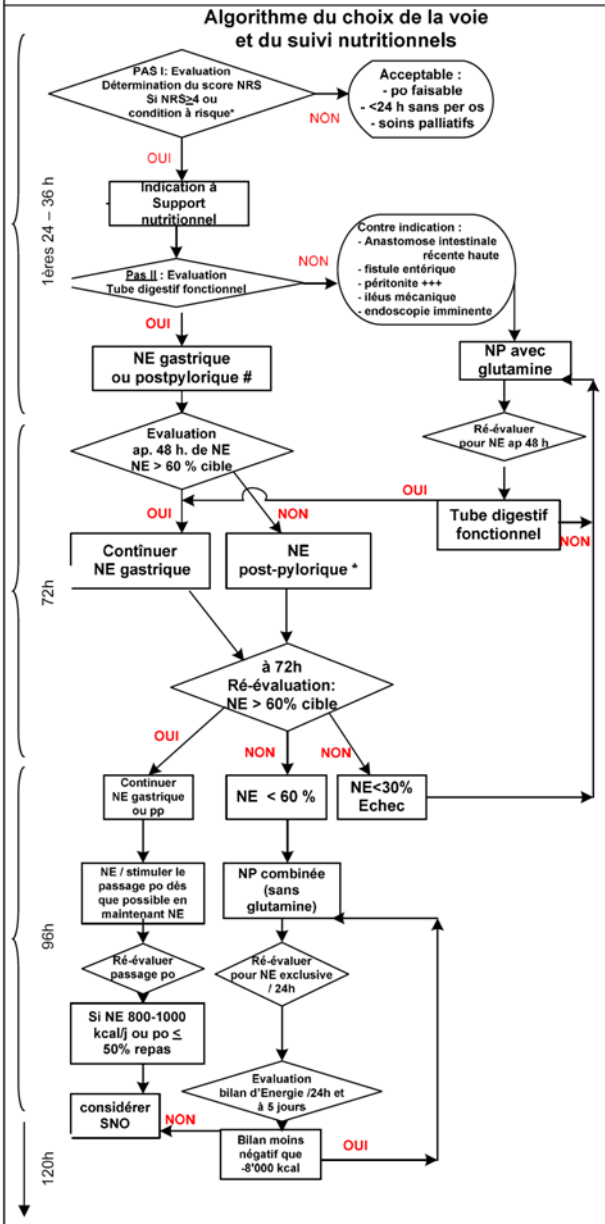
Sévérité modérée :SI « light » = NEMS < 21	2 points
Sévérité importante : SI « lourd » = NEMS > 20	3 points

C. Age du patient (0 à 1 point)

< 70 ans	0 point
≥ 70 ans	1 point

Score NRS-2002 = Total des points : pire score A + B + C (0 à 7 points)

1. B. Choix du support nutritionnel

Déroulement	Commentaire
Algorithme du choix de la voie et du suivi nutritionnels 	**Pas I :** **Préalable à l'évaluation** : connaissance du poids pré-admission, de la taille du patient et des apports antérieurs pour déterminer les risques nutritionnels * : polytrauma, brûlé, dénutri Détermination **des besoins en énergie (cible)** se fait en parallèle, basé sur le protocole nutrition **Pas II: Eval. du tube digestif** **Pas III : Choix de la voie nutrition** • NE : §3 • NP et combinée: §4 • N. orale / suppléments : §5 **Pas IV : Choix des solutions nutritives** • NE: Promote® Fibres Plus • NP: Alisia (Olimel E 5.7%® le WE ou pour N. combinée) • Oral : normal / SNO **# PostPylorique (PP) précoce indications = jéjunostomie en place, brûlé > 40%BSA pancréatite sévère** *** PP à 72h indications = échec de gastrique** **Pas V : Prescription et surveillance** **Ré-évaluation quotidienne du tube digestif, car son état varie dans le temps chez le patient de réanimation** **SNO : maximum 3 par jour, entre les repas** **Pas VI : Résultats** **Bilan d'énergie quotidien** **Bilan de laboratoire hebdomadaire** • Bilan d'énergie cumulé: < -8'000 kcal (équiv. -100 kcal/kg) Si NE progresse bien et bilan moins négatif : continuer NE si NE difficile et bilan plus négatif : nutrition combinée

1. C. Bilans métaboliques lors de nutrition artificielle y.c. perfusion de Propofol®, et séjours > 48 heures au SMIA

	Lundi	Mercredi	Vendredi
Patient aux soins intensifs > 48h, sans support nutritionnel	Triglycérides	Triglycérides	Triglycérides
Patient sous NE (sauf brûlé)	Triglycérides CRP Albumine + Préalbumine Bilirubine totale + directe ASAT + ALAT Gamma-GT Phosphatase alcaline Créatinine + Urée Ca^{++} Mg Phosphate	Triglycérides	Triglycérides
Patient sous NP	Idem *Patient sous NE* ↑	Triglycérides	Triglycérides Bilirubine totale ASAT + ALAT Gamma-GT Phosphatase alcaline Créatinine Urée Ca^{++} Mg Phosphate
Patient brûlé sous NE	Idem *Patient sous NE* ↑ + dosage du Calcium et Créatinine **urinaire** (urines 12h) si séjour > 2 semaines + Cu, Se, Zn sanguin sur indication diététicienne	Triglycérides	Triglycérides

Dans les catégories à risque (brûlés, polytraumatisés, patients sous épuration extrarénale, drains abdominaux divers, pancréatites), des dosages d'éléments pourront s'avérer nécessaires et seront demandés par l'équipe de nutrition au cas par cas.