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Interactions médicamenteuses et réactions adverses aux soins intensifs: Le rôle des sédatifs et des analgésiants

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Résumé

Les patients admis aux soins intensifs (SI) souffrent de comorbidités qui affectent leur pronostic. Deux problèmes sont potentiellement associés aux sédatifs et compliquent le séjour de 35 à 50% des malades : le délirium, un état confusionnel aigu; et le coma 'iatrogénique', une altération de la conscience induite pharmacologiquement. L'importance de l'association entre clinique et médicaments a un intérêt pour prévenir ces syndromes cliniques morbides.

Nous voulions étudier le délirium et le coma iatrogénique, les doses administrées de midazolam et de fentanyl, leurs niveaux plasmatiques, les variantes génétiques de métabolisme et de transport et les facteurs inflammatoires et ce, chez 100 patients admis aux soins intensifs. Nos données soulignent l'importance des interactions médicamenteuses dans l'incidence du coma iatrogénique, et réfutent l'association entre les benzodiazépines et le délirium. Ces résultats clarifient la pathophysiologie du délirium, corroborent le manque d'association délirium-benzodiazépines avec un marqueur biologique, c.-à-d. les niveaux sériques, et ouvrent le débat quant aux agents les plus utiles pour traiter l'anxiété et le délirium. Finalement, plusieurs caractéristiques pharmacocinétiques des benzodiazépines administrées aux soins intensifs publiées récemment complètent les données de notre étude quant à la sédation en soins critiques. Un chapitre sur l'importance de la pharmacogénomique en soins intensifs et un débat publié quant au pro et con de l'utilisation des benzodiazépines aux SI, sont soumis en complément de l'étude clinique décrite ci-haut effectuée dans le cadre de cette maîtrise.

Mots-clés : délirium, coma, sédation, soins intensifs, opiacés, benzodiazépines, pharmacologie, interactions médicamenteuses, cytochrome P-450, réaction médicamenteuse adverse

Abstract

Critically ill patients suffer from co-morbid conditions that impact on their prognosis. Two problems complicate Intensive Care Unit (ICU) stay in 35-50% of patients and are potentially associated with sedatives: delirium, an acute confusional state, and 'iatrogenic' coma, when consciousness is altered pharmacologically. Establishing the association between these clinical syndromes and administering sedatives is key in planning effective prevention of these morbid complications.

We studied iatrogenic delirium and coma in 100 ICU patients given midazolam and/or fentanyl, and tallied drug doses, measured plasma levels, genetic variations in metabolism and transport and inflammatory factors. Our data highlight the role drug-drug interactions play in iatrogenic coma, and refute the association between benzodiazepines and delirium. These results clarify the pathophysiology of delirium, corroborate the lack of delirium-benzodiazepine association with a benzodiazepine biological marker, i.e. serum levels, and open the debate as to which agents are useful for treating anxiety and delirium. Recent publications addressing benzodiazepine pharmacokinetics in critical care complement our data in the field of critical care sedation. A chapter on the importance of pharmacogenomics in intensive care, and a published pro-con debate as to benzodiazepine use in critical care are submitted in addition to the clinical study mentioned above as part of this master's thesis.

Keywords: Delirium, Coma, Critical care, Sedation, Opiates, Benzodiazepines, drug interactions, Pharmacology, Cytochrome P-450, Adverse Drug Reaction

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Avant-propos

Le contexte des soins intensifs est particulier. Des milliards dépensés en soins de santé, les soins hospitaliers coûtent le plus cher [1]. Les bénéficiaires les plus malades survivent grâce aux technologies déployées dans les unités de soins intensifs (USI), notamment la ventilation mécanique. Les USI sont les unités les plus dispendieuses dans un milieu hospitalier, constituant 20% des budgets institutionnels[2]. Au Canada et aux États-Unis, ces coûts représentent 1% du Produit Intérieur Brut [3]. Les patients sous ventilation mécanique plus de 5 jours coûtent le plus cher et occupent 45% de la totalité des journées d'admissions hospitalières [4, 5]. En outre, la plus grande proportion du budget de la pharmacie hospitalière (20 à 38%) est dépensée aux USI [6]. Les complications associées à ces médicaments sont morbides et dispendieuses[7]. Les effets indésirables (EI), dont les interactions médicamenteuses, sont décrites chez 6,7% des patients hospitalisés, augmentent le coût et les complications associées aux soins, et sont décrites comme étant deux fois plus fréquentes chez les patients des USI [8].

Les sédatifs et les analgésiants sont communément administrés aux patients aux soins intensifs, tout particulièrement à ceux sous ventilation mécanique. Leur but est de rendre cette expérience, ainsi que la souffrance associée à leur maladie critique, plus tolérables. Ces mêmes médicaments se classent cependant parmi les six (6) principales catégories de médicaments responsables des EI, complications coûteuses et évitables [9] aux soins intensifs.

Les coûteuses modalités de réanimation employées par les soignants en soins intensifs ont été considérées efficaces en termes de la survie des malades, le critère principal jusque récemment de mesure des résultats espérés. Pourtant, la probabilité de décès n'est pas nécessairement le seul critère de devenir qui intéresse les malades, car ceux-ci (et leurs proches) sont tout aussi préoccupés par l'état dans lequel ils se retrouvent s'ils survivent [10]. À titre d'exemple, peu sont informés que chez les survivants ayant nécessité une ventilation mécanique de 5 jours ou plus, 6 mois après leur congé hospitalier, 50% manifestent des symptômes de perturbation de santé mentale (dépression, syndrome post-traumatique, dysfonction cognitive) [11-13]. Ces séquelles sont associées à des stigmates humains et économiques importants, tant pour ces patients que pour leurs familles (57% en sont

dépendants un an après leur congé[11]). Ces conséquences sont d'autant plus inattendues que la promesse de la technologie menant à une récupération totale semblait assurée à la case départ.

Il est donc temps d'incorporer d'autres critères de devenir que la mortalité aux études aux soins intensifs. Ce changement de paradigme nous mène au développement d'études en pharmacologie clinique, spécifiquement quant aux sédatifs et aux analgésiants[14], car une meilleure compréhension du meilleur choix d'agent dans cette population onéreuse et vulnérable risque d'améliorer les prises de décision en fonction du coût et des séquelles (en qualité de vie ou autres paradigmes) associées aux interventions proposées.

L'impact économique des médicaments aux soins intensifs

Les médicaments font partie du coût direct d'un séjour aux soins intensifs. Jusque trente-huit pour cent (38%) du budget de la pharmacie hospitalière y est dépensé [15]. Les déboursements médicamenteux aux soins intensifs sont ceux dont le taux d'augmentation a été le plus rapide (12% en trois ans) en comparaison aux coûts de médicaments ailleurs qu'aux soins intensifs (6%) entre 1999 et 2002[15]. L'utilisation d'agents pharmacologiques implique aussi des coûts indirects : les effets indésirables reliés aux médicaments augmentent tant le séjour aux soins intensifs que le coût hospitalier; celui des soins intensifs est particulièrement onéreux, s'élevant entre $1500 et $3500 par jour [3, 4, 6]. Ces effets indésirables sont deux fois plus fréquents aux soins intensifs, et sont mal documentés. Qui de plus est, la sédation ainsi que les doses de médicaments sédatifs et analgésiants administrés durant le séjour aux soins intensifs sont associées à la durée d'hospitalisation. Tous ces éléments soulignent l'importance de se pencher sur ces interventions pharmacologiques, et d'y incorporer des analyses pharmaco-

économiques rigoureuses. Lors de notre tentative de décrire les conséquences économiques de l'adoption d'un protocole pour les analgésiants et les sédatifs prescrits en fonction de symptômes de patients individuels, pratique qui n'est pas appliquée dans tous les établissements, l'absence de données économiques directes du réseau de santé québécois ont constitué une limitation importante à notre évaluation [16]. Nous avons cependant pu démontrer une économie moyenne de $1000 par patient lorsque les médicaments étaient administrés uniquement en fonction des besoins objectivés de douleur et d'agitation [16]. Peu d'études ont spécifiquement examiné les enjeux économiques associés aux médicaments administrés au patient de façon longitudinale, en évaluant les coûts associés à l'hospitalisation, au payeur, et en incorporant les coûts sociétaux. Idéalement, toute évaluation pharmaco-économique ne se limiterait pas au séjour hospitalier, mais établirait une mesure des coûts réels des soins du système de santé; en plus des coûts médicamenteux et hospitaliers on devrait tenir compte des réadmissions hospitalières, du besoin de réhabilitation en centre, à la maison, ou des soins de longue durée, la reprise d'emploi de la part du patient et de ses proches, et des besoins en infrastructures autres (physiothérapie, psychologue, achat d'équipements spéciaux). L'utilisation des sédatifs et des analgésiants (particulièrement les opiacés) est reliée à toutes ces dimensions des soins critiques, et peu de données existent pour étoffer une analyse complète des dimensions économiques reliées à leur usage.

La dysfonction cérébrale

Deux pathologies aiguës sont, depuis une dizaine d'années, reconnues comme étant des complications graves d'un séjour aux soins intensifs: les anomalies cognitives et les atteintes de l'état de conscience. En l'absence d'une anomalie structurelle (comme une hémorragie

cérébrale ou un accident cérébro-vasculaire, par exemple) on parle de délirium (une anomalie de cognition) ou de coma iatrogénique (atteinte de l'état de conscience reliée aux médicaments administrés). Ces deux anomalies ont été décrites par certains comme une manifestation d'un spectre de dysfonction cérébrale [17], donc une atteinte progressive et incrémentale au cerveau. Elles sont décrites plus en détail ci-dessous. Ces explications servent de mise en contexte pour l'étude publiée dans Critical Care Medicine présentée dans ce mémoire, et pour cadrer leur importance en lien avec les médicaments sédatifs et analgésiants administrés.

Le délirium

Le délirium qui survient aux soins intensifs mène à une mortalité accrue, à un séjour hospitalier prolongé et à un taux d'institutionnalisation élevé suite à cette hospitalisation chez les survivants[18]. Les patients plus malades, hypertendus, fumeurs et alcooliques sont plus à risque de le développer [18]. Nos premières études sur le délirium[19] suggéraient que la sédation lourde et le coma qui y étaient associés le prédisaient[18]. Nous espérions diminuer l'incidence de ce coma par sédation excessive et, par conséquent de l'association, l'incidence du délirium. Nous avons développé un protocole pour limiter l'administration de sédatifs et d'opiacés strictement selon des échelles de douleur et d'anxiété et d'agitation, afin d'arrimer les besoins au traitement individuel et pour éviter l'administration excessive de ces agents [20]. Le taux de coma fut réduit de 20 à 7% ; le délirium sous-syndromal [21], un état entre la normalité et le délirium franc, a diminué et le taux de retour à domicile sans perte d'autonomie s'est amélioré[20]. Le taux de délirium est cependant resté inchangé. Nous pensions que, bien qu'il fût possible que le taux réel de délirium n'ait pas changé, il était plus probable que le taux ait en fait diminué et que l'éveil accru des patients comateux avant la diminution des médicaments avec le protocole ait démasqué des patients dont le délirium était indétectable lorsqu'ils étaient inconscients. La présomption véhiculée dans la littérature depuis plus de 20 ans que les médicaments sédatifs (les benzodiazépines) et analgésiants (opiacés) sont associés au délirium est cependant demeurée intacte.

Une des possibilités peu envisagées dans notre travail à l'époque, et dans la littérature en général, était que le diagnostic de délirium n'était pas aussi précis avec une échelle clinique validée que ne pouvait l'être, par exemple, une variable biochimique comme un niveau de

cholestérol. Même chez les patients ambulatoires et communicatifs, la validité des critères diagnostiques pour les maladies psychiatriques varie selon les critères utilisés et le(la) diagnosticien(ne)[22]. L'identification du délirium est hétérogène. Les critères diagnostiques de délirium selon le DSMIV ont été établis à partir de patients ambulatoires ou dans des populations hospitalisées gériatriques stables, donc différents de ceux aux soins intensifs. Si ces normes ne sont pas établies à partir de patients admis aux USI, l'applicabilité de ces critères peut donc être remise en question [23] chez des patients dont les médicaments sédatifs et opiacés peuvent avoir un effet psychotrope. Le délirium aux USI se distingue de celui décrit dans toutes les autres populations pour plusieurs aspects: 1) l'âge ne confère pas de risque alors que c'est le contraire dans d'autres populations[18], 2) ses caractéristiques psychomotrices se manifestent par une part égale de délirium hypoactif et agité en contraste avec les déliriums hypoactifs, agités[24] ou mixtes décrits dans d'autre populations, et 3) la description de sa prévalence varie énormément, soit de 10% à plus de 80%[25], laissant croire que son identification n'est pas une chose simple. En pratique, une identification fiable de patients à haut risque pour le délirium [26] à des fins de prévention ou d'intervention précoce n'est pas très pratique à cause de cette problématique d'ordre méthodologique au niveau du diagnostic. Cependant, une étude comme celle décrite dans le cadre de ce mémoire de maîtrise, où un seul outil est utilisé de façon reproductible dans une population relativement homogène, peut révéler des caractéristiques très claires associées aux médicaments, par exemple, alors que cela n'aurait peut-être pas été le cas avec une autre échelle de dépistage ou en tentant de mener une étude multicentrique sans vérifier la corrélation entre intervenants lors de l'application des échelles.

Certains outils de dépistage du délirium ont été spécifiquement développés pour les patients admis aux USI. L'Intensive Care Delirium Screening Checklist (ICDSC), développé à l'hôpital Maisonneuve-Rosemont [27] à Montréal, est maintenant utilisé à travers le monde[28-32] et recommandé dans les directives pour la gestion de la douleur, de l'agitation et du délirium (publié par la Society of Critical Care Medicine américaine en janvier 2013)[33]. Cette échelle développée et validée pour le dépistage du délirium chez les patients aux USI compte 8 items qui reflètent les symptômes cliniques en temps réel. Les syndromes vont d'aucune anomalie (dans 20 à 30% des patients) à un délirium subsyndromal [21] (30%

des patients) et finalement au délirium franc. En outre, la présence de symptômes individuels de l'ICDSC prédit certains résultats fonctionnels [24] comme le retour à la maison.

Le délirium est un signe avant-coureur de mauvais pronostic clinique, comme la durée de séjour aux soins intensifs, hospitalière ainsi que la mortalité [18, 34]. L'association à la ventilation mécanique[35] ou aux séquelles neuropsychiatriques comme les réactions de stress post-traumatique, de dépression à court terme et d'un dysfonctionnement cognitif à long terme est, pour le moment, mal étoffée[36]. L'impact du délirium sur les proches aux soins intensifs est aussi peu étudié, mais il est probable que, tout comme dans d'autres populations, le délirium du patient est associé à une détresse de ses proches [37] à court et moyen termes. Les symptômes associés au délirium aux soins intensifs diminuent la probabilité d'un retour à domicile en pleine autonomie[21].

L'ajout d'un commentaire au sujet de la dysfonction cognitive est de mise ici. Il s'agit de la complication que craignent le plus les patients et leurs proches. La littérature décrivant le devenir cognitif après une hospitalisation de soins intensifs est très hétérogène. Dix-neuf études de qualité acceptable ont été publiées à ce jour et ont récemment fait l'objet d'une revue systématique[38]. L'incidence d'anomalies cognitives graves et persistantes semble s'élever autour de 45-62% chez les survivants aux soins intensifs. L'association au délirium n'est pas établie. La seule publication qui semble l'appuyer souffre d'éléments confondants importants[39] ; on n'a pas tenu compte, par exemple, de la superposition des facteurs de risque qui prédisent les anomalies cognitives, e.g. la vasculopathie et l'hypertension, et des facteurs de risque les plus importants pour le délirium aux soins intensifs, dont l'hypertension est en tête de liste.

Le coma iatrogénique

Les sédatifs sont administrés à presque tous les malades aux soins intensifs pour atténuer leur perception d'une expérience désagréable. Cette routine se solde, en pratique, par une proportion significative de patients qui répondent uniquement aux stimuli douloureux, ou sont inconscients. Dans quelques pathologies rares comme le syndrome de détresse respiratoire aiguë (SDRA), qui représente 5% de toutes les admissions aux soins intensifs [40],

une sédation profonde s'impose en raison de l'hypoxie sévère. Cependant, 75% des patients ventilés mécaniquement sont plongés en coma à l'admission et pendant les 48 heures subséquentes [41, 42]. Les conséquences de coma iatrogène à la suite de l'administration de sédatifs ne sont pas bénignes. Les conditions qui y mènent et leurs mécanismes sont donc cruciaux pour établir les circonstances de cette conséquence nocive de ces médicaments, qui doit désormais être identifiée comme effet médicamenteux indésirable.

La validation rigoureuse depuis 1999 des premières échelles de sédation appliquées aux soins intensifs permet de mesurer le niveau d'apaisement et/ou d'anxiété, et de mieux ajuster les médicaments administrés. Le Richmond Agitation-Sedation Scale [43] (RASS) et la Sédation-Agitation Scale [44] (SAS) sont valides et fiables en réanimation adulte, et sont recommandées dans les lignes directrices décrivant la gestion optimale courante de la douleur, de l'agitation et du délirium [45] de la Society of Critical Care Medicine. Ce choix s'appuie sur le fait que même si d'autres échelles existent, la validation psychométrique de la SAS et RASS est supérieure en termes des critères usuels de fiabilité inter-évaluateurs, de validation convergente ou discriminante, et ce, dans diverses populations en soins intensifs. Des niveaux de RASS de -4 et -5 correspondent à des patients qui réagissent à la douleur profonde (-4) ou pas du tout (-5), et sont équivalents aux scores SAS de 1 et 2.

Les échelles de sédation décrites ci-dessus sont utilisées de routine dans les unités de soins intensifs québécoises et canadiennes. Lors d'administration de sédatifs et d'opiacés, et en l'absence d'autres facteurs pathologiques tels que des lésions neurologiques, les patients qui deviennent comateux à cause de l'administration de substances pharmacologiques peuvent donc être identifiés comme souffrant de coma iatrogénique. Nos données récentes[46] ainsi que celles de collègues canadiens[47] suggèrent que les niveaux sériques des opiacés ainsi que ceux des sédatifs comme le midazolam (molécule-mère et ses métabolites) sont associés au niveau (c.-à-d. à la profondeur) de cette sédation clinique. Le coma iatrogénique peut donc être considéré comme une absence de réponse aux stimuli sur une échelle d'évaluation de sédation standardisée, avec des niveaux plasmatiques de médicaments sédatifs ou d'opiacés élevés lorsqu'ils sont comparés aux niveaux des patients sans coma.

La diminution de l'état de conscience, qu'elle soit brève ou de durée moyenne, est associée à une morbidité accrue, à une augmentation de la mortalité et à des coûts plus élevés que les

soins des patients avec lesquels un contact est maintenu [16, 18]. Les données provenant d'études au suivi longitudinal [48] associent la diminution de l'état de conscience médicamenteux avec une augmentation de la mortalité[18] et de la durée prolongée de la ventilation et de séjour en soins intensifs[49].

L'interruption des perfusions de sédatifs, leur ajustement et la minimisation de la quantité de médicaments administrés est associée à un bénéfice net pour le patient, à une plus courte durée de ventilation mécanique, et à une réduction des coûts[16] sans pour autant aggraver le stress psychologique [50]. Les recherches évaluant les modalités de sédation aux soins intensifs, ainsi que les lignes directrices sur cet aspect de la pratique, préconisent l'optimisation et l'individualisation de la sédation en fonction des besoins ciblés pour chaque patient, en contraste avec l'approche d'une «dose standard» véhiculée dans le passé. Les recommandations récentes du Society of Critical Care Medicine préconisent maintenant une sédation légère ou, lorsque c'est impossible, une interruption régulière des doses de sédation administrées[45]; les deux approches étant équivalentes [51] dans la minimisation des doses administrées et dans les bénéfices notés dans le devenir de ces patients ayant eu des doses de médicament diminuées. Même lorsque l'ajustement soigneux des médicaments en fonction des symptômes n'est pas possible (chez les patients paralysés, en hypertension intracrânienne ou hypoxiques) la minimisation des doses administrées comporte quand même un bénéfice [52]. Nous avons démontré que, même avec un ajustement prudent, l'incidence de coma iatrogène diminue, mais demeure aux alentours de 7% ; l'ajustement des médicaments ne réduit l'incidence du coma que du niveau initial de 18% à 7%, donc un peu plus de la moitié [16]. Ce paradoxe apparent justifie une enquête plus approfondie sur les mécanismes de survenue de coma.

Factors predisposing to coma and delirium: Fentanyl and midazolam exposure, *CYP3A5*, *ABCB1* and *ABCG2* genetic polymorphisms, and inflammatory factors.

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ABSTRACT:

Delirium and sedative-induced coma are described as incremental manifestations of cerebral dysfunction. Both may be associated with sedative or opiate doses and pharmacokinetic or pharmacogenetic variables such as drug plasma levels (exposure), drug metabolism, and/or their transport across the blood brain barrier.

Objectives: To compare biological and drug treatment characteristics in patients with coma and/or delirium while in intensive care.

Patients and Measurements: In 99 patients receiving intravenous fentanyl (FEN), midazolam (MDZ) or both, we evaluated drug doses, covariates likely to influence drug effects (age, BMI, renal and hepatic dysfunction), delirium risk factors, concomitant administration of CYP3A and P-glycoprotein (P-gp) substrates/inhibitors, *ABCB1* (P-gp), *ABCG2* (BCRP) and *CYP3A5* genetic polymorphisms, and FEN and MDZ plasma levels. Delirium and coma were evaluated daily. In patients with only coma (n=15), only delirium (n=7), and neither ever (n=14) we measured plasma levels of: Tumor Necrosis Factor alpha (TNF α), Interleukin (IL) 1β, IL-1ra, IL-6, IL-8, IL-10, IL-17, Macrophage Inflammatory Protein (MIP)-1β and Monocyte Chemotactic Protein-1 (MCP-1).

Results: Time to first coma was associated with FEN and MDZ doses (p=0.03 and p=0.01, respectively). The number of days in coma was associated with the number of days of co-administration of CYP3A inhibitors (r=0.30; p=0.006). Plasma levels of FEN were higher in

patients with clinical coma (3.7±4.7 *vs.* 2.0±1.8 ng/ml, p=0.0001) as were MDZ plasma levels (1050±2232 *vs.* 168±249 ng/ml, p=0.0001). Delirium occurrence was unrelated to midazolam administration, cumulative doses or serum levels. Days with delirium were associated with days of co-administration of P-gp inhibitor (r=0.35; p=0.0004). Delirious patients had higher levels of the inflammatory mediator IL-6 than comatose patients (129.3 *vs.* 35.0 pg/ml, p=0.05).

Conclusions: Coma is associated with FEN and MDZ exposure; delirium is unrelated to midazolam and may be linked to inflammatory status. These data suggest that iatrogenic coma and delirium are not mechanistically linked.

INTRODUCTION:

Delirium, a fluctuating disturbance of consciousness and cognition, is common in acute illness. Coma, a reduction in the level of consciousness, is often associated with sedative or opiate administration. Delirium and medication induced coma are common and morbid in the critically ill. Delirium occurs in 35% to 70% of all intensive care (ICU) patients [1,2] and is associated with significant complications and cost.[3,4] Iatrogenic coma (i.e. when deep sedation occurs inadvertently) is also associated with morbid short and long term outcomes, mortality, and expenditure.[2,5,6,7] Why some patients become delirious, or develop iatrogenic coma, is unclear. Coma and delirium are described by some as progressive states of cerebral dysfunction, or 'brain failure' in the ICU setting.[8] However, the link between delirium and iatrogenic coma in the adult critically ill patient is not well established or understood.

The synthetic opioid fentanyl (FEN) and the benzodiazepine sedative midazolam (MDZ) are commonly administered in the critical care setting [9] and are extensively metabolized by the same CYP450 isoenzymes, namely, CYP3A4/5.[10,11] Co-administration of FEN and MDZ, or of either FEN or MDZ with other drugs metabolized by the CYP3A4/5 isoenzyme [12] may increase serum or tissue drug levels because of competitive inhibition, and these increases may influence the development of either delirium or coma. Further, genetic polymorphisms are associated with the functional level of expression of these enzymes (especially CYP3A5) [13,14] which may also modulate the central nervous system effects of MDZ or FEN.

Several sedative and opiate drugs are substrates for blood-brain barrier (BBB) influx/efflux transporters such as P-glycoprotein (P-gp, MDR1), breast cancer related protein (BCRP) or isoforms of multidrug resistance related proteins (MRP1, MRP2, MRP4).[15,16,17,18,19] Accumulation of these drugs or drug metabolites in the brain might lead to neurotoxicity and clinical delirium. Therefore, variations in the phenotypic activity of BBB transporters due to genetic polymorphisms or competitive inhibition may determine one's susceptibility to these side effects.[20]

Finally, inflammatory mediators may also modulate sedative and opiate effects on the brain, and influence clinical coma and delirium. Abnormalities in inflammatory mediators are linked to delirium.[21] Limited information exists as to the effect of inflammatory mediators on the function and integrity of the BBB. Elevated serum levels of inflammatory mediators

might affect the distribution (passive diffusion) or transport of FEN and MDZ by affecting BBB permeability and transport. In addition, inflammatory mediators influence CYP 3A4/5 activity[22].

Our focus was drug-induced coma and delirium in the ICU. Many mechanisms have been invoked in their pathogenesis, but four are specific to the critical care setting and were at the heart of this study: 1) alteration in systemic drug exposure due to changes in functional drug metabolism caused by drug-drug interactions or underlying diseases, 2) the presence of drug metabolism-related genetic polymorphisms, 3) blood brain barrier transport variability, associated with polymorphisms in related genes, 4) variability in inflammatory mediator expression. Our aim was to explore the relationship between the clinical occurrence of delirium and coma and these four variables, in a group of critically ill adults receiving FEN and/or MDZ.

In a consecutive series of critically ill adults with delirium, iatrogenic coma, neither or both, we performed ongoing clinical assessments during their ICU stay, documented all relevant medications, measured plasma levels of FEN and MDZ, and determined genetic *CYP3A5*, *ABCB1* (P-gp), and *ABCG2* (BCRP) genetic polymorphisms. We also determined FEN and MDZ serum levels, as well as levels of inflammatory mediators in patients who had only delirium, only coma or neither to study the association between inflammatory mediators and these clinical events observed in ICU.

Methods:

1. Description of the cohort and studied parameters:

100 adult consenting patients admitted to ICU for over 24 hours and receiving intravenous FEN or intravenous MDZ were recruited. Patients were considered ineligible for the study if they had had cerebral anoxia, if they presented with a central nervous system lesion which could cause or mimic coma; all other neurological pathologies were included. We evaluated administered drug doses of FEN and MDZ, FEN and MDZ plasma levels, previously described delirium risk factors,[2] covariates likely to influence drug effect (age, body mass index (BMI), ethnic origin, gender, renal and hepatic dysfunction), ICU length of stay (LOS), concomitant administration of CYP3A and P-gp substrates and inhibitors, as well as *CYP3A5, ABCB1* and *ABCG2* genetic polymorphisms. Clinical outcomes (delirium and coma) were

evaluated daily. This study, including the genotype sampling, was reviewed and accepted by the Ethics Board of the Maisonneuve-Rosemont Hospital and conducted in accordance with their ethical standards. Informed consent was formally obtained from surrogates, and also requested from patients themselves in the presence of their next of kin whenever patients were awake and lucid. Whenever feasible, all obtained consents were confirmed by directly asking the patient for consent again once they were discharged to the ward. None of the patients entered in this study were part of any other cohort or participated in any other trial.

ICU patients were evaluated every 8 hours by nurses and/or physicians using pain (Numerical Rating Scale, or, in patients unable to self-report, Behavioural Pain Scale assessments), sedation (The Richmond Agitation-Sedation Scale (RASS) [23] and delirium scales (Intensive Care D Screening Checklist (ICDSC)).[24]. Coma was considered present when the RASS score was -4 or -5, and associated with MDZ or FEN if these drugs were being administered in the absence of other sedatives such as propofol, or confounding neurological pathology or neuromuscular blockade. Coma at any time was treated as a binary variable: presence or absence of coma. Delirium symptoms were stratified: ICDSC scores of 0 to 3 represented no delirium; a score of 4 or more was considered delirium. Delirium at any time was treated as a binary variable (presence or absence).

Liver function abnormalities and renal failure assessments were based on routinely drawn daily blood samples. AST and ALT levels 1.5 times the normal values were considered abnormal, and calculated or measured creatinine clearances below 50 ml/min were considered abnormal. The pharmacological profiles (presence or absence of co-administered medications) were documented daily. All sedatives and anti-psychotics were tallied in all patients. All substrates of equal or greater affinity for the same CYP 450 isoenzyme as midazolam or fentanyl, i.e. medications known to be significant CYP3A4/5 substrates or inhibitors (the cytochromic pathway known to influence midazolam and fentanyl metabolism) were considered; these are listed in Supplementary Table S1. All medications potentially associated with blood brain barrier permeability because of P-gp substrate/inhibitor effect are also listed. CYP 450 inducers (as shown on the table) were considered; only 15 patients received them for a fraction of their ICU stay and no effect was found on study endpoints.

2. Statistical analysis:

Baseline characteristics on admission were expressed as mean ± standard deviation or median (interquartile range: IQR) for continuous variables and frequencies and percentages for categorical variables. Baseline characteristics were compared between patients who developed coma and/or delirium and patients who did not using chi-square test for categorical variables while continuous variables were compared using Student t-test or Mann-Whitney test if distributional assumptions were not met. Mean FEN and MDZ plasma levels in patients with coma vs. not were compared with t-tests.

Coma and associated variables

Correlations between the number of days in coma and the number of days of CYP3A and P-gp inhibitor co-administration were assessed using Spearman correlations.

In order to incorporate additional variables such as FEN and MDZ presence and doses, Cox models were used to model time to first occurrence of coma with the following features as time-dependent explanatory variables:

- presence vs. absence of FEN, and doses of FEN
- presence vs. absence of MDZ, and doses of MDZ
- presence vs. absence of CYP3A4/5 inhibitors and presence vs. absence of P-gp inhibitors.

Since patients with coma had a mean ICU stay of 17.5 days (in contrast with patients who did not, whose mean was 8.2 days) , and given the covariates associated with coma, generalized Estimating Equations (GEE) were used to model daily presence of coma with the following features as time-dependent explanatory variables:

- administered doses of fentanyl
- administered doses of midazolam
- presence of CYP3A4/5 inhibitors (given to 40 patients, temporarily or intermittently)
- presence of P-gp inhibitor

Finally, a total of 197 FEN and MDZ serum levels were sampled; we considered all patients and one patient could be sampled in one of more of the described clinical states. In patients with clinical coma 105 samples were collected; 35 were drawn while the patients had delirium, and 57 while the patient experienced neither. Mean plasma FEN and MDZ levels

were compared between patients with coma, patients with delirium and those with neither coma nor delirium; two or more of these samples could come from a single patient at a different moment of their ICU stay. Mean plasma FEN and MDZ levels were also compared between patients who experienced coma (but never delirium) during their ICU stay while they were comatose and patients who never experienced coma in the ICU. These mean values were compared with an unpaired t-test.

Delirium

Similar Cox analyses as described above were carried out for patients who developed delirium and patients who did not. GEE analyses were carried out for daily presence of delirium only with regard to midazolam, to confirm the interaction between midazolam and delirium occurrence, as patients with delirium had shorter lengths of stay than patients with coma.

Inflammatory mediator analysis

Levels of inflammatory mediators were compared in patients with either only coma, only delirium, or neither ever, whose blood samples were drawn within 24 hours of that clinical state. As the levels of inflammatory mediators were not normally distributed, they were described using median (IQR) and compared using the non-parametric Kruskal-Wallis test followed by pairwise Mann-Whitney tests in case of significant findings.

Genotyping methods, inflammatory mediator analysis, and MDZ and FEN plasma measurements are described in the supplementary material S2.

RESULTS:

1) Description of the cohort:

Patient characteristics are described in Table 1. One patient's clinical data was entered incorrectly; this data was removed. All patients were included in the delirium analysis. No patient had coma without FEN or MDZ. Fifteen patients developed coma while receiving FEN or MDZ with intravenous propofol; they were excluded from the coma analysis because propofol may have contributed to the coma. As-needed haloperidol (range 1-10 mg/day) was the only other administered psychotropic medication. The screening and inclusion of patients is described in Figure 1. The high incidence of both delirium (60%) and coma (56%) in this cohort is in keeping with the high incidence of both pathologies in the general critical care

literature, and with the patients' severity of illness, multiple co-morbidities, and length of ICU stay. Apache scores were similar in patients with coma (21.5±8.1 (p=0.55 vs. no coma)), with delirium (20.1±7.8 (p=0.9 vs. no delirium) or with neither (17.7±4.7).

Patients were sedated lightly (average RASS of -0.4); sedatives and analgesics were titrated to symptoms [25] but not routinely interrupted. In our overall cohort, mean ICU length of stay (LOS) was 14.3±12.9 days (mean±SD) with a median of 10 days (range 2-79 days). Patients experienced their first coma or delirium on average on day 3.2 and 7.6 days in ICU, respectively. Patients' characteristics were comparable between groups (Table 1).

2) CYP3A5, ABCB1 (P-gp) *and ABCG2* (BCRP) *genetic polymorphism distribution:*

Distribution of the *CYP3A5, ABCB1 3435C→T* and *ABCG2 C→A* polymorphisms were not related to clinical outcome, as described in Table 2.

3) Association between clinical variables and incidence of coma or delirium:

Correlation of clinical variables with incidence of coma:

Coma occurred at least once in 56 patients. Gender, age, APACHE II score, BMI, alcohol consumption, renal dysfunction, *CYP3A5, ABCB1* and *ABCG2* genotypes were unrelated to coma (Table 1 and 2). Smokers were more prevalent in patients presenting with coma, as were patients with hepatic dysfunction.

First coma

Coma occurred within a mean of 3.22±3.44 days after the initiation of FEN or MDZ.). Time dependent Cox regression models revealed that time to first coma was associated with incremental doses of FEN and MDZ received prior to coma (p=0.03 and p=0.01, respectively) and to the presence of either drug (p=0.005 and p=0.01 for FEN and MDZ respectively). Patients receiving both FEN and MDZ developed coma sooner than did patient receiving either FEN or MDZ (mean days to coma 0.81 vs. 0.69, p=0.0045). CYP3A4/5 inhibitors may have played a role (p=0.09) but P-gp inhibitors did not (p=0.3). Whether coma occurred was unrelated to current (last 24 hours) FEN dose (p=0.419), and to current MDZ dose (p=0.52).

Coma over time in the ICU

The number of days in coma in patients with coma was independently associated with the number of days of co-administration of CYP3A inhibitors (r=0.30; p=0.006) but not with the co-administration of P-gp inhibitors (p=0.17) with Spearman correlations. In patients with clinical coma, and in those with no coma, unpaired T-test comparison of mean FEN plasma levels suggested higher values in patients with coma (3.7±4.7) *vs.* those without it (2.0±1.8 ng/ml, p=0.0001). Similarly, comatose patients had higher MDZ plasma levels in comparison to non-comatose patients (1050±2232 *vs.* 168±249 ng/ml, p=0.0001, Figures 2A and 3A). Similar differences were found between when patients were analyzed considering whether they had ever had an episode of coma while in the ICU or not (FEN: 3.4±3.7vs. 1.8±1.5, p=0.006; MDZ 1001±2223 vs. 156±205, p=0. 032, Figures 2B and 3B). The distribution of FEN and MDZ plasma levels on a graph with bars depicting comatose and non-comatose patients reveals a shift of the curve in FEN and MDZ levels to the left in non-comatose patients, in keeping with their lower concentrations of these drugs (Figures 2C and 3C). GEE modeling suggested a_correlation between coma duration and FEN doses (p=0.0078) and MDZ doses (p=0.0072).

Correlation of clinical variables with incidence of delirium:

Delirium occurred at least once in 62 patients. Gender, age, APACHE II score, BMI, alcohol consumption, renal dysfunction, CYP3A5, ABCB1 and ABCG2 genotypes were unrelated to delirium (Table 1 and 2).. On Cox analysis, time to first occurrence of delirium was unrelated to administered doses of midazolam (p=0.4), and presence of midazolam (p=0.3). The relationship between the number of days in delirium and the number of days with CYP3A or P-gp inhibitors were tested with Spearman correlations; P-gp inhibitors were associated with delirium (r=0.35; p=0.0004). GEE revealed that the duration of the first episode of delirium was not associated with concomitant MDZ administration (p=0.25783) or with cumulative MDZ administration (p=0.96). The days in delirium over the ICU stay were also not associated with MDZ doses on delirium days (p=0.25) or with cumulative MDZ dose (p=0.96). FEN plasma levels were similar in patients with and without delirium (3.2±3.5 ng/ml vs. 2.7±3.6 ng/ml; p=0.4). MDZ levels were lower in patients with delirium than in patients without delirium (217±279 ng/ml vs.555±1539 ng/ml; p=0.001).

Inflammatory mediators association with coma or delirium:

In the 36 patients who presented with either only iatrogenic coma (n=15), only delirium (n=7), or neither (n=14) during their ICU stay and who had blood samples drawn within 24 hours of that clinical state, we measured the levels of several inflammatory mediators with biologically plausible association to delirium or coma. No differences were found in the levels of inflammatory mediators between the cohorts for TNF-α, IL-17, IL-8, MCP-1, IL1-RA, MIP-1β and IL-10 (Table 3). The median levels of IL-6 was 129.3 pg/ml (IQR: 48.8 to 291.7) in delirium patients *vs.* 35.0 pg/ml (IQR: 11.3 to 78.5) in comatose patients (p=0.05). Notably, all (100%) delirious patients had plasma concentrations of IL-6 greater than 40 pg/ml while only 5 of the 15 (33%) comatose patients reached that IL-6 concentration. Only 1 out of 15 comatose patients (7%) and 4/14 (29%) of the normal patients had an IL-1β concentration above the detection level while 57% (4/7) of the delirious patient had detectable levels of IL-1β in their plasma.

DISCUSSION:

Coma and delirium are clinically morbid. Understanding their pathophysiology may change practice and improve care. Objective biologic or clinical evidence do not support the assumption that delirium and coma are part of a spectrum.

In this prospective study, we investigated the pharmacologic and inflammatory characteristics of patients presenting with coma or with delirium, and asked whether these characteristics are similar or different in comatose and delirious patients. We assessed the incidence of coma and delirium in 99 patients admitted to ICU for 24 hours or more who received intravenous FEN, MDZ or both. We also evaluated the administered dose of these two drugs, plasma FEN and MDZ levels, the co-administration of CYP3As and P-gp inhibitors, the presence of covariates likely to influence drug effects, the presence of important *CYP3A5, ABCB1* (P-gp) and *ABCG2* (BCRP) polymorphisms and plasma levels of key inflammatory mediators.

Our first major finding was that coma is indeed associated with duration, but not daily dose, of drug exposure (FEN and MDZ) whereas delirium is not. Second, we observed higher FEN and MDZ serum levels in comatose patients, and an association between days in coma and days with CYP3A4/5 inhibitors. This suggests that both drug-drug interaction (e.g. co-administration of drugs competing for the same CYP 450 isozymes leading to higher plasma levels), and drug accumulation (since duration of FEN administration, but not dose, was

longer in patients who developed coma) play a role in coma occurrence. Third, we also observed that delirium is unrelated to midazolam exposure, but appears to be influenced by a more pronounced systemic inflammatory status (IL-6). Although it is widely believed that delirium and coma are mechanistically linked, our results suggest that in critically ill patients these two entities have very different etiologies.

An association is proposed between benzodiazepine administration and delirium in critically ill patients.[26,27,28,29] Because continuously sedating patients with MDZ appears associated with a higher incidence of delirium than sedating patients with dexmedetomidine,[30] and because this difference is not seen when morphine is compared to dexmedetomidine,[31] MDZ was presumed to be linked to delirium occurrence. The Confusion Assessment Method (CAM-ICU) screening tool for ICU delirium used in these studies may, however, be confounded by sedation. High MDZ serum levels have also been described in delirious septic patients,[32] albeit heavily sedated ones. In the current study, despite the widely held assumption that midazolam may worsen delirium, MDZ levels were lower in patients with delirium than in patients without delirium (217±279 ng/ml vs.555±1539 ng/ml; p=0.001). MDZ was not associated with delirium occurrence despite multiple analyses considering its administration prior to delirium, total doses administered, MDZ plasma levels or duration of administration. These results strongly contrast with beliefs currently held by critical care clinicians and scientists, whose recommendations that MDZ be avoided because it is 'deliriogenic'[33] may not take into account the pharmacokinetic interactions between co-administered drugs or alterations in metabolism linked to other critical illness co-morbidities [34].

FEN and MDZ compete for the same CYP450 isozymes (CYP3As) for metabolism [35,29] with a potential decrease in drug clearance. The increased plasma levels of the drugs we observed are most probably associated with this phenomenon. Unsurprisingly, we found an association between FEN and MDZ levels and the presence of coma. MDZ can act synergistically with FEN to produce coma-like symptoms,[35,36] in keeping with the earlier coma observed in our patients receiving both medications. When given concomitantly, only 25% of the median Effective Dose (ED_{50}) of FEN is required in combination with 23% of the ED_{50} for MDZ to achieve the ED_{50} of this drug combination.[35] However, critical care physicians do not currently routinely lower FEN or MDZ dosage when prescribing these drugs concomitantly[37].

We measured inflammatory mediators known to be involved in the regulation of the BBB permeability, and thus potentially associated with coma and/or delirium. IL-1β [38] and IL-6 [39,40,41,42,38], both linked to increased BBB permeability, appear associated with delirium in our population. Transport of morphine metabolites across the BBB is influenced by Central Nervous System IL-6 in critically ill patients [43]. Other cytokines did not correlate with clinical coma or delirium to a statistically significant degree, but the study may have been underpowered to detect their role. IL-17 contributes to BBB dysfunction [44] in mice; anti-inflammatory IL-1 receptor antagonist (IL-1RA) and IL-10 also appear associated with BBB dysfunction.[45,46]. One small study found an association between IL-8 levels and ICU delirium [21]. We believe this is the first report of an association between inflammatory mediators and delirium in the context of MDZ or FEN administration.

Whereas FEN is a substrate of P-gp,[47,29] MDZ is not (or is at most only a very weak substrate of this transporter) [16]. MDZ accumulation in the brain is therefore likely to occur with or without the co-administration of P-gp inhibitors, while drug interactions will affect FEN transport if other BBB transporters do not compensate P-gp activity changes. These drug characteristics may explain the lack of association observed in our study between the administration of P-gp inhibitors and the occurrence of coma; however, since delirium and coma vary over time, and since administered drug doses also vary over the duration of ICU stay, potentially complex associations cannot be established with clarity in our population.

The associations of our covariates with clinical manifestations of delirium were more challenging to interpret. Although an association with the co-administration of BBB transport inhibitors (P-gp inhibitors) was found, the effect was only marginal ($R=0.35$), albeit highly significant ($p=0.004$), pointing to the complexity of the interactions of the diverse factors invoked in association with ICU delirium.[48] To our knowledge, this is the first reported association between P-gp inhibitors and delirium.

We acknowledge that our study has some limitations. Our relatively small sample size prevented us from performing more elaborate statistical analyses. We did not measure the alpha hydroxy metabolite has of midazolam, which has nearly 2/3 of the GABA receptor site affinity as the parent drug and accumulates with renal dysfunction.[49] The relatively infrequent sampling of inflammatory mediators over time precluded associating change of these mediators with clinical signs and symptoms. Nonetheless, the significant differences in

the factors associated with either coma or delirium in such a small sample size is, in itself, meaningful. We also recognize that several other biological, pharmacological and complex pharmacokinetic factors may have direct or indirect effects on the occurrence of the described pathologies in our patients. The strengths of the study include a broad representation of critically ill patients and the correlation of pharmacological interventions with well-established clinical indices of disorders of cognition and/or consciousness. Administered FEN and MDZ were validated with clinical effect and pharmacokinetic data. This information may serve as a springboard for further studies to better understand the pathophysiology of coma and delirium, and the influence pharmacological management has on these diseases.

Nevertheless and while considering these limitations, the differences in the clinical characteristics associated with coma and with delirium, respectively, are striking. Both delirium and coma are associated with significant morbidity and mortality, and are increasingly being associated with long-term cognitive and psychological sequelae.[3,50] One of our major findings is that coma was associated with FEN and/or MDZ drug administration, and FEN and/or MDZ plasma levels, while delirium was not. This finding is important for two reasons: 1) understanding the epidemiology and the mechanistic aspects of coma and delirium as separate pathologies will help clinicians and scientists predict, prevent and possibly treat both entities; 2) coma and delirium were described as a combined 'brain failure' outcome in important publications.[51,52], and these data suggest that the two clinical presentations are not part of a similar pathology. Curtailing sedation may reduce coma and 'prevent acute and chronic brain dysfunction' [53], a preventative approach recently integrated into recommendations adopted by several institutions and societies.[54,53] If coma and delirium are in fact distinct, such recommendations should be made to reduce coma, but would not be expected to reduce the incidence of delirium. Further studies may better elucidate the association between pharmacologic management and delirium.

Iatrogenic coma and delirium do not appear to be mechanistically linked. Coma appears to be associated with drug exposure while delirium, on the other hand, may be associated with systemic inflammation.

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CONFLICT OF INTEREST/DISCLOSURE:

The authors report no conflict of interest.

Table 1: Characteristics of patients (n=99) enrolled at entry to the intensive care unit. Patients' characteristics were comparable between groups (delirium, coma, in comparison to neither) in terms of delirium risk factors such as APACHE II score, smoking, alcohol consumption, and hypertension, and in terms of features potentially affecting drug metabolism such as liver or renal dysfunction, age, and body mass index. P values compare patients with coma to patients without coma, and patients with delirium to patients with no delirium. As patients could present both coma and delirium during one hospital stay, the groups are not mutually exclusive.

	Coma	**Delirium**	**None**
Number of patients	59	64	12
% of male patients	55.4 (p=0.7)	48.4 (p=0.34)	58.3
Age (years)	63.2 ±14.2 (p=0.17)	62.0±13.9 (p=0.34)	55.2±15.7
APACHE II score	21.5±8.1 (p=0.55)	20.1±7.8 (p=0.9)	17.7±4.7
BMI	27.7±6.5 (p=0.26)	28.1±7.3 (p=0.49)	23.8±4.0
% of smokers	40.7 (p=0.03)	34.4 (p=0.33)	16.7
% of alcohol consumers	35.6 (p=0.29)	29.7 (p=0.61)	16.7
% with hepatic dysfunction	20.3 (p=0.06)	18.8 (p=0.07)	10.3
% with renal dysfunction	37.3 (p=0.24)	35.9 (p=0.26)	16.7

BMI: Body Mass Index; Smoker (%): percentage of patients smoking 20 or more cigarettes per day; Alcohol (%): percentage of patients drinking more than 7 or 14 drinks per week for women or men, respectively; Hepatic dysfunction (%): percentage of patients presenting with an ALT level 1.5 times higher than normal; Renal dysfunction (%): percentage of patients presenting with a creatinine clearance below 50µg/ml. Patients with coma include the 84 patients receiving only MDZ or FEN or both; the 16 patients concomitantly receiving propofol, a potential confounder in inducing coma in critically ill sedated patients, were excluded from the analysis between coma and no coma.

Table 2:
Distribution of the *CYP3A5, ABCB1 3435C→T* and *ABCG2 C→A* polymorphisms according to clinical outcome. Groups (coma vs. none, and delirium vs. none) were compared with Pearson chi-square. P values refer to proportion of genetic polymorphism distribution in patients with coma vs. no coma or delirium; or delirium vs. no coma or delirium.

No *CYP3A5 *1/*1or ABCG2 AA* polymorphisms were found in this cohort, in agreement with the expected frequency in our population; in 525 French Canadians 1.0% were homozygous (*421AA*) for the variant and 14% heterozygous (*421CA*).(26)

The frequency of *CYP3A5*1/*3* heterozygotes (10.8%) is in accordance with literature reports.(24) In our cohort, the *ABCB1 3435 C→T* polymorphism was in Hardy-Weinberg equilibrium with the frequency of the variant allele ranging from 34% to 55%, which is also in accordance with published literature.(19).

ABCB1(MDR1) activity was considered high (wt/wt or CC), intermediate (wt/mutation ot CT) or weak (TT).

Genetic polymorphism							
	*CYP3A5 *1/*3*	*CYP3A5 *3/*3*	*ABCB1 C/C*	*ABCB1 C/T*	*ABCB1 T/T*	*ABCG2 C/C*	*ABCG2 C/A*
Coma N (%)	6 (10.9%)	49 (89.1%)	15 (27.3%)	29 (52.7%)	11 (20.0%)	50 (84.7%)	9 (15.3%)
P value coma	p=0.34		p=0.58			P=0.93	
Delirium N (%)	7 (11.7%)	53 (88.3%)	14 (23.3%)	32 (53.3%)	14 (23.3%)	55 (85.9%)	9 (14.1%)
P value delirium	p=0.14		p=0.93			p=0.72	
No coma or delirium N (%)	2 (5.1%)	37 (94.9%)	12 (30.8%)	19 (48.7%)	8 (20.5%)	30 (83.3%)	6 (16.7%)

Table 3: Median (IQR: interquartile range) serum levels (pg/ml) of inflammatory mediators in relation to clinical state in three mutually exclusive sub-groups of the 99 patient cohort.

	Only Coma	**Only Delirium**	**None**	**Delirium vs. Coma**
n=	15	7	14	P value
TNF-α	2.6 (1.7-18.7)	5.2 (3.4-23.0)	6.8 (3.4-14.4)	NS
IL-1β	1.3 (1.3-1.3)	1.3 (1.3-3.9)	1.3 (1.3-2.2)	0.07
IL-17	3.9 (3.0-3.9)	3.9 (3.9-6.8)	3.0 (2.1-3.9)	NS
IL-8	25.4 (6.3-61.3)	15.7 (10.0-65.5)	27.1 (10.0-87.0)	NS
MCP-1	199.2 (79.6-550.6)	354.3 (163.9-700.7)	205.8 (67.6-477.7)	NS
IL-1RA	2,652 (1,323-12,503)	10,427 (5,891-14,540)	6,214 (1,386-12,914)	NS
IL-10	11.6 (8.0-28.9)	11.4 (1.6-18.3)	8.0 (1.6-12.9)	NS
MIP-1β	45.0 (20.1-74.7)	62.9 (50.7-89.0)	35.3 (15.1-79.6)	NS
IL-6	35.0 (11.3-78.5)	129.3 (48.8-291.7)	48.7 (16.5-915.4)	0.05

Tumor Necrosis Factor alpha (TNF α), Interleukin (IL) 1β, IL-1ra, IL-6, IL-8, IL-10, IL-17, macrophage Inflammatory Protein (MIP)-1β and Monocyte chemotactic protein-1 (MCP-1) values were compared. IQR: interquartile range. NS: non-significant.

Figure 1: Study flow and patient outcomes

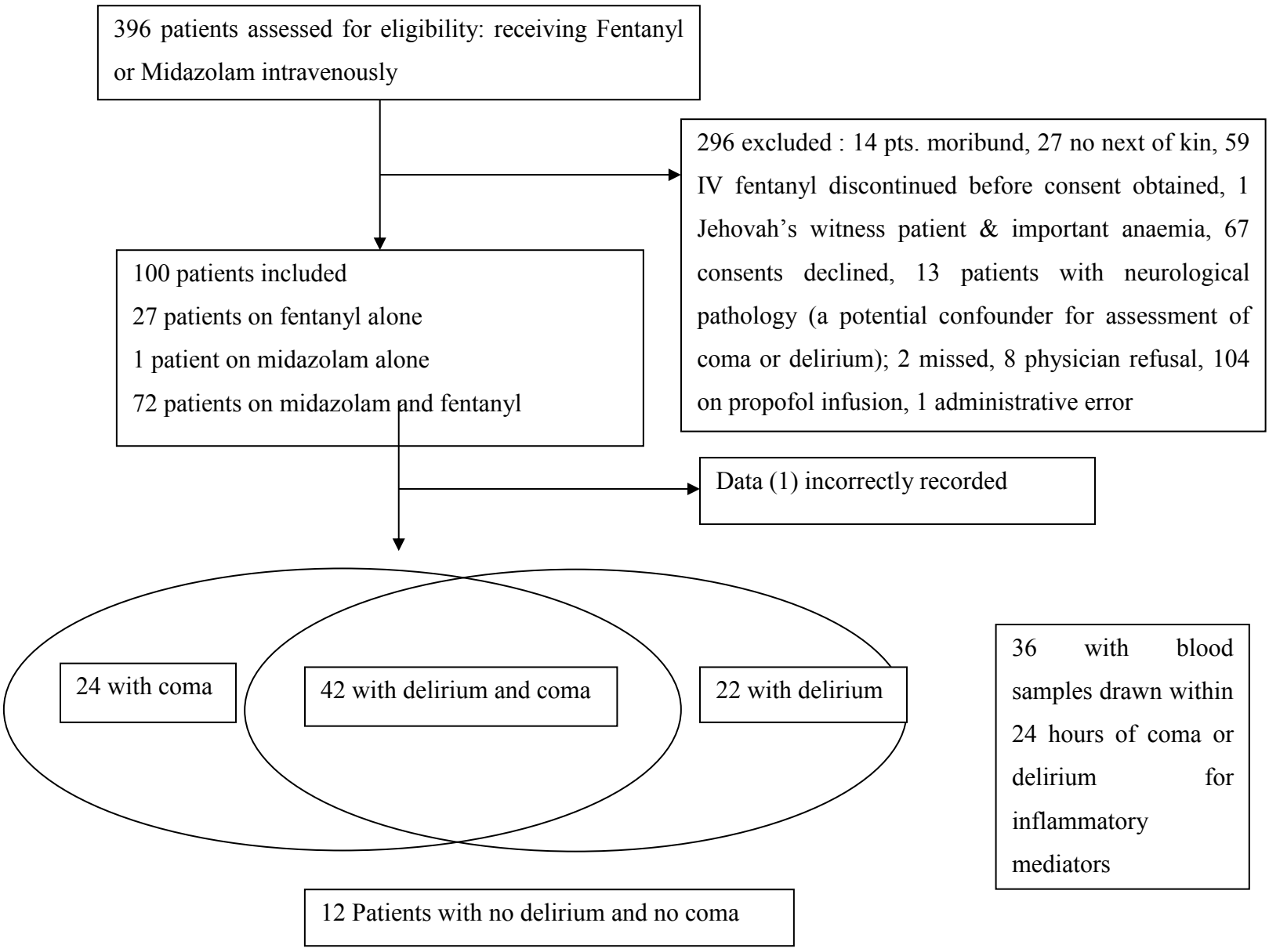


Figure 2:

A) Plasma Fentanyl (FEN) concentrations drawn in patients during comatose status *vs.* plasma levels in patients with no coma at the time of serum sampling; all patients were included and the same patient could figure in both groups (i.e. when comatose and when not comatose). Patients without coma have significantly lower FEN levels. Statistical significance is illustrated with an asterisk.

B) The concentrations of FEN were compared in patients who never developed medication associated coma, and those who did. The results remain similar to the previous analysis, confirming the association between drug level and clinical effect (coma). Statistical significance is illustrated with an asterisk.

C) This graph illustrates the profile of distribution of FEN concentrations of patients with and without coma, and shows a shift towards the left for patients without coma (in keeping with their lower drug concentration level).

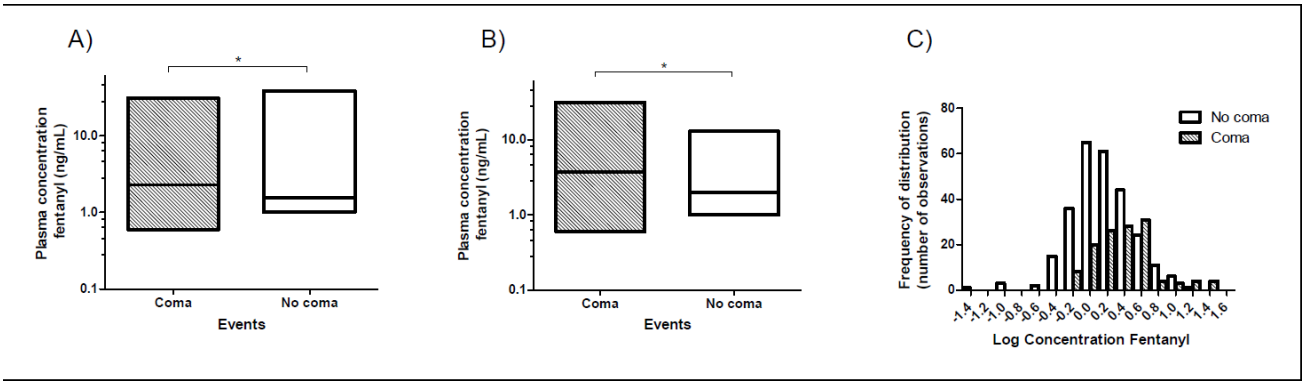
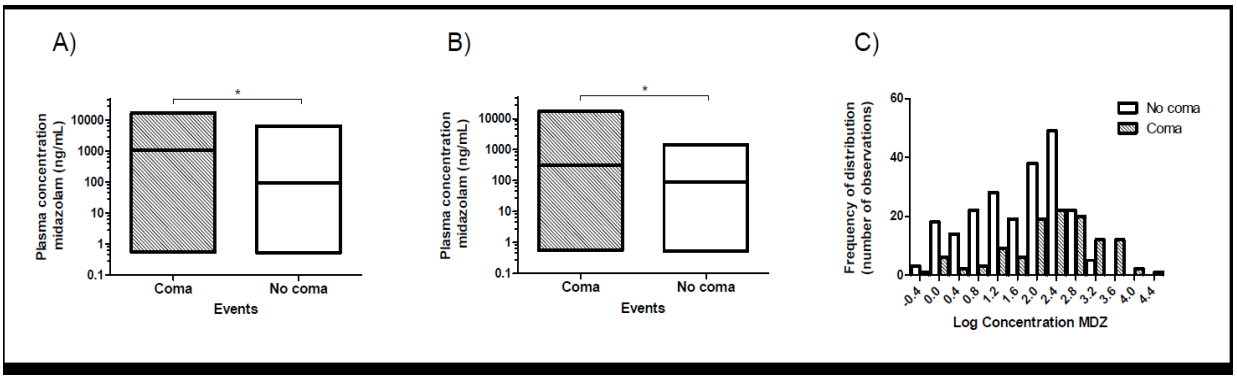


Figure 3:

A) Plasma midazolam (MDZ) concentrations drawn in patients during comatose status *vs.* plasma levels in patients with no coma at the time of serum sampling; all patients were included and the same patient could figure in both groups (i.e. when comatose and when not comatose). Patients without coma have significantly lower MDZ levels. Statistical significance is illustrated with an asterisk.

B) The concentrations of MDZ were compared in patients who never developed medication associated coma, and those who did. The results remain similar to the previous analysis, confirming the association between drug level and clinical effect (coma). Statistical significance is illustrated with an asterisk.

C) This graph illustrates the profile of distribution of MDZ concentrations of patients with and without coma, and shows a shift towards the left for patients without coma (in keeping with their weaker drug concentration level).



Conclusion

L'étude présentée dans le cadre de ce mémoire décrivant 100 patients admis aux soins intensifs qui ont reçu par voie intraveineuse du midazolam, fentanyl, ou les deux, souligne quelques aspects de la pharmacologie en milieu de soins intensifs immédiatement intégrables à la pratique clinique. Parmi les soixante-six patients qui ont développé un coma iatrogénique, des doses de médicaments sédatifs semblables à celles administrées aux patients éveillables avaient été administrées avant la survenue du coma. Les concentrations plasmatiques de midazolam, de fentanyl ou des deux étaient cependant plus élevées chez les patients ayant présenté un phénotype de coma. Le nombre de jours dans le coma a été associé avec le nombre de jours de co-administration d'inhibiteurs des CYP3As, l'isoenzyme responsable du métabolisme du fentanyl et de midazolam, ce qui suggère un mécanisme d'interaction médicamenteuse (EI) pour expliquer cette baisse de l'état de conscience. Des taux plasmatiques élevés de midazolam en combinaison avec une sédation prolongée ont été associés à un pronostic de soins intensifs plus sombre [18] par un autre groupe canadien. Ces résultats ajoutent au savoir quant aux mécanismes auxquels le coma iatrogénique peut être attribué en milieu de soins critiques. La sédation lourde est problématique et morbide. Éviter la coadministration de médicaments pour lesquels une interaction est documentée ou réduire les doses lors de cette coadministration pourrait améliorer le taux de coma et le devenir des malades.

Nos données sur ce petit échantillon de patients suggèrent fortement, cependant, que le mécanisme de toxicité cérébrale n'en est pas un de continuum de 'dysfonction cérébrale' (où le coma et le délirium font partie d'un éventail de symptômes de sévérité progressive) tel que décrit par d'autres auteurs. Il est probable que la toxicité associée au métabolisme ou au transport de médicaments sédatifs et analgésiques qui caractérise les patients inconscients admis aux soins intensifs critiques est liée à l'effet neurologique d'une sédation profonde, mais aussi aux interactions médicamenteuses, ce qui rendrait cette complication évitable. Tant la mécanistique du développement de cette sédation que l'évaluation d'une autre pathologie potentiellement reliée à une autre forme de neurotoxicité (augmentation de la perméabilité de la barrière hémato-encéphalique et diffusion accrue de métabolites toxiques au travers d'une

membrane rendue perméable par l'inflammation) sont d'un grand intérêt pour les cliniciens. Le rôle joué par les métabolites et leur vitesse d'élimination, élaboré dans le chapitre et l'article de revue ci-dessus, complète les informations suggérées dans le projet de recherche original.

Le lien entre les sédatifs, les analgésiants et la dysfonction cérébrale

Le délirium est un problème commun et dépistable aux soins intensifs ; les échelles créées pour ce faire sont applicables même auprès de patients incapables de s'exprimer verbalement, tels les patients ventilés mécaniquement. Cependant, les critères diagnostiques sont basés sur des études de validation dans des populations ambulatoires. Il est donc possible que ce qu'on appelle délirium aux soins soit en fait, en partie, un effet pharmacologique. La différentiation entre l'effet médicamenteux et un état psychiatrique est souvent difficile à faire.

Il semble clair qu'il n'y a pas de lien entre l'administration de benzodiazépines et la survenue d'un délirium aux soins intensifs. Ces informations sont importantes compte-tenu du coût minime des benzodiazépines (1/70 à 1/300ième du prix des autres molécules[1]) et du manque d'interventions pharmacologiques efficaces pour le délirium. En effet, le manque d'efficacité des antipsychotiques, l'agent le plus utilisé, est maintenant reconnu. Nos résultats ouvrent la possibilité d'utiliser les benzodiazépines comme agents pour le délirium, en plus de mitiger les craintes à l'égard de leur utilisation. Finalement, la toxicité potentielle des métabolites des benzodiazépines, particulièrement dans le contexte d'une barrière hemato-encéphalique plus perméable dans un contexte inflammatoire, pourrait expliquer l'agitation ou l'altération de l'état de conscience observée chez une proportion des patients et ainsi, expliquer également les différentes présentations et incidences de ce qu'on appelle un délirium aux soins intensifs.

Le mariage des connaissances pharmacologiques et cliniques aux soins intensifs a de nombreux avantages. Plusieurs caractéristiques pharmacologiques sont altérées dans une population de patients instables et critiques comparativement à d'autres types de malades ou de sujets sains. Ces différences au niveau du métabolisme et du potentiel d'interactions médicamenteuses ont un effet direct sur les soins quotidiens. Il est question d'un milieu où les dépenses sont énormes, où chaque modification et amélioration, et son analyse pharmacoéconomique, implique un avantage sociétal potentiel. L'avenir de cette avenue de recherche incorpore les notions de santé personnalisée et de devenir cognitif, de santé mentale et de qualité de vie.

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Publications annexes au mémoire

Pharmacogenomics and cerebral dysfunction

Chapitre de livre accepté pour publication dans Brain Disorders in Critical Illness, Cambridge University Press

Yoanna Skrobik MD FRCP(c)

Executive summary

More medications are administered in critical care units than in most hospital wards; ICU pharmacy expenditures often approach 20% of a hospital pharmacy's budget. The cost of this level of care is complicated by adverse events (AEs) that increase costs even further. Adverse drug reactions (ADRs) occur in 6.7% of hospitalized patients[1], and are twice as common among the critically ill[2]. Many quality assurance initiatives have been proposed to mitigate other costly pharmacy-performance related issues, such as medication administration errors. In contrast, ADRs require an understanding of pharmacokinetics and pharmacogenomics.

Sedatives and opiate analgesics are routinely administered in severely ill and mechanically ventilated patients, and rank among the top 6 medication categories responsible for ADRs in critical care[3, 4]. The therapeutic efficacy and the toxicity associated with the metabolism or transport of sedative and analgesic medications, on one hand, and neurologic findings such as deep sedation or coma, and delirium, are linked. The mechanistic pathway rationale for this association, and clinical examples and data supporting that these interactions occur and are or may be clinically significant, are presented in this chapter.

Key words: critical care, intensive care, pharmacokinetics, drug-drug interactions, adverse drug reactions, sedation, sedatives, analgesia, analgesics, coma, delirium

Introduction

Severe adverse drug events relevant to critical care practitioners were described in 1957[5] with the rare but dramatic complication of succinylcholine administration to inherited butyrylcholinesterase variant carriers[6]. The 1 in 3500 affected Caucasians with a genetically determined single amino acid substitution[7] develop severe complications after the short term paralytic agent succinylcholine is administered. The following decades have brought better understanding of genetic determinants of drug metabolism; publications addressing pharmacogenomics have increased further since the completion of the human genome project [6] (figure 1). Genetically or metabolically influenced drug-drug interactions, alterations in metabolic pathways and variable pharmacokinetics are understood and described in many clinical settings. Most of these reports, however, focus on cardiovascular or oncologic drugs[8] . Complex drug interactions in other patient populations can lead to dramatic complications such as respiratory failure and coma[9]. This type of complication requires critical care admission, and should be familiar to the intensive care caregiver. In addition, multiple and often interacting drugs are administered in the critical care setting, highlighting the relevance of pharmacology and drug interaction related clinical effects, such as confusion and coma, to the critical care practitioner.

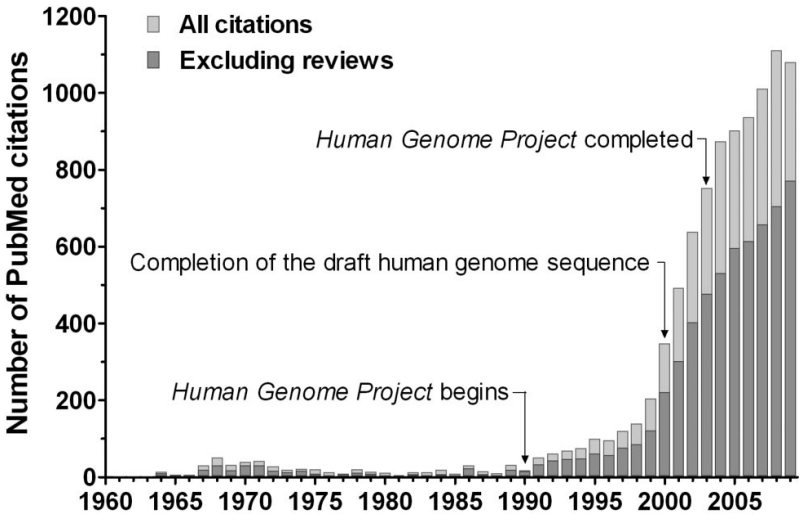

Figure 1. The emergence of pharmacogenomics. Number of citations including the terms pharmacogenetics or pharmacogenomics in PubMed are plotted vs. year. A dramatic

increase is observed paralleling advances in technology and the completion of the Human Genome Project. Adapted from Meyer [6] .

Many drug interactions and genetic variants affect consciousness and cognition. Caregivers administer sedation to mitigate the patient's perception of the ICU experience; significant proportions of patients respond only to pain or are unresponsive. Patients with acute respiratory distress syndrome, who account for 5% of ICU admissions [10], may require deep sedation because of severe hypoxia. However, coma-like sedation levels occur in 75% of mechanically ventilated patients [11-13]. Sedative metabolism changes associated with age make this deep sedation, which can be considered a pharmacological complication, more likely[14]. Short or medium term decreases in consciousness in ICU are associated with increased morbidity, mortality, and expenditure[12, 15-17]. Follow-up studies[18] associate decreases in consciousness with increased mortality[15, 19], prolonged duration of both ventilation and ICU stay[12], neuropsychological dysfunction[20] and functional decline[21-23]. Either interrupting or titrating[24] and minimizing drug administration benefits patients, shortens mechanical ventilation duration, reduces costs[25] and does not worsen psychological stress[26]. Current ICU sedation research and practice recommendations [27, 28] therefore advocate optimizing and individualizing sedation goals. However, careful symptom-driven drug dosing is not always possible. In addition, even with careful protocol driven sedation and analgesia, iatrogenic coma incidence is reduced only by half [29]. This apparent paradox suggests that ICU patients' pharmacokinetic and pharmacodynamic characteristics differ from those described in patients receiving short-term sedatives and analgesics for general anesthesia or in the procedural context.

Drug-metabolizing enzymes: Cytochrome P450 enzymes

Cytochrome P450s (CYP) are a superfamily of 57 hepatic enzyme coding genes that metabolize many drugs. Cytochrome pathways are responsible for the metabolism of most medications administered in critical care. Enzymes of drug metabolism pathways, including CYP 450, are subject to genetic polymorphisms that may alter their metabolic activity. The

genetic polymorphism of these enzymes thus plays a significant role in their metabolic activity and should be taken into account when administering these drugs, although there is a dearth of information as to the impact of genetic polymorphisms in critical care. Slow, intermediate, fast and ultra-fast metabolizers have been described with, in some of the clinical examples described within the chapter below, dramatic clinical consequences. Genetic polymorphisms thus explain some of the drug response variability between individuals. Regulation of CYP activity is primarily transcriptional: nuclear receptors are recognized as key mediators in drug metabolism enzyme modulation. Their ligands are both endogenous and exogenous substances, which may have an agonistic or antagonistic effect on these transcription factors. The protein structure within different cytochromes determines affinity, and therefore specificity, for various substrates. Some substrates modify biotransformation enzyme activity; by increasing or decreasing it, they are classified as inducers or inhibitors. Co-administration of medication, a common occurrence in critical care, whether agonist or antagonist nuclear receptor ligands, can lead to severe toxicity, loss of therapeutic efficacy or to metabolic imbalance. Thus, CYP activity is dependent on both genotype and the environment.

The CYP3A system is the most abundantly expressed; more than 50% of medications in clinical use are isoenzyme CYP3A substrates[30, 31].CYP3A4 and CYP3A5 are its principal isoforms. CYP3A4/5 determines the metabolism of many therapeutic agents, among them midazolam, fentanyl, and antifungal agents such as fluconazole. The concurrent administration of drugs metabolized by this pathway leads to increases in serum drug levels and to potentiated therapeutic effect in studies conducted outside the intensive care unit (ICU)[32]. Excessive sedation is known to occur when benzodiazepines such as midazolam, triazolam, alprazolam or diazepam, or non-benzodiazepine sedatives such as zopiclone and buspirone, are administered with CYP3A4 inhibitors[33]. Published expert reviews describe cytochrome P450's importance as a critical determinant of drug clearance, and as involved in the mechanism of numerous clinically relevant drug-drug interactions observed in critically ill patients[34]. However, these biological and pharmacological premises are not supported by many clinical descriptions. Indeed, and despite sound rationale that these interactions should

and do occur, data are sparse as to what effects occur and the extent to which they are clinically significant.

The few clinical descriptions that drug interactions exist in the ICU and have an impact in day to day clinical practice are nevertheless compelling. One example of potentially significant interactions is depicted in figure 2 (prototypical individual patient, unpublished data). Mathematical modeling to project expected fentanyl levels based on administered doses and infusion rates failed to predict the measured fentanyl levels when fluconazole was being co-administered (such as the individual whose values in hours 0-50 are shown in figure 2). The higher fentanyl levels correlated with deep sedation. The effect was no longer present with similar fentanyl doses once fluconazole was discontinued (> 100 hours, figure 2). How constant this effect is across cohorts and with different CYP 450 3A4 inhibitors is not known.

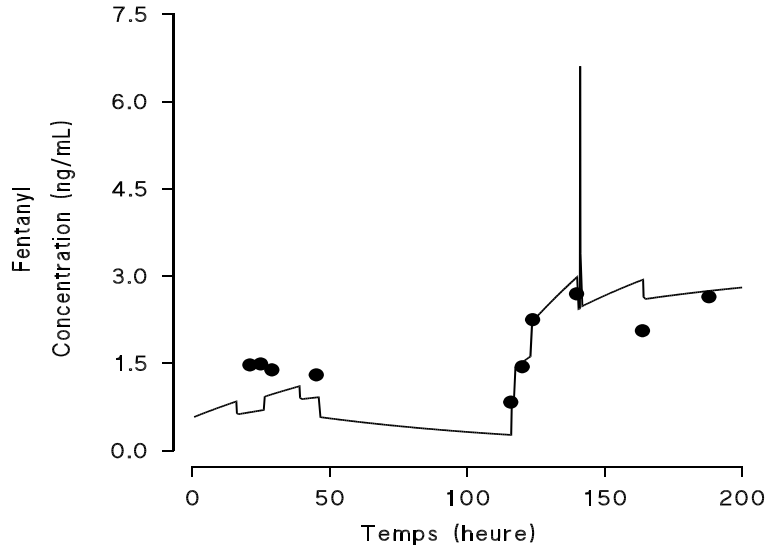

Figure 2: mathematical modeling fit during administration of fluconazole (0-50 hours) vs. after fluconazole cessation in an ICU patient receiving intravenous infusions of fentanyl. The measured fentanyl serum level was nearly the double of the projected level when a medication competing for the same metabolic pathway was given concurrently.

Computerized cytochromic interaction alerting software exists to identify potential drug interactions in vulnerable populations receiving multiple medications. It has been shown to improve detection and adjustment of medication based on identified interactions in geriatric patients[35]. In 100 elderly patients receiving five or more medications, a total of 238 cytochrome P450 drug-drug interactions were identified, of which over 70% involved CYP3A4. Medication adjustments and follow up were deemed to be required in over 50% of the patients based on the information provided by the software. Similar smart alert or detection systems have not been tested to date in critically ill adults, or correlated with clinical outcomes.

The CYP3A5 variant is present in 10% or so of the Caucasian population[36, 37] but in as many as 30% or more African Americans. Such patients metabolize CYP450 3A4 pathway drugs more quickly[38]. Midazolam requirements, sedation levels and serum midazolam measurements were compared in critically ill patients homozygous for this polymorphism, and in critically ill heterozygotes[39]. No significant differences were found. Whether a difference might be detected if CYP3A5 *1/*1, CYP3A5 *1/*3 and CYP3A5 *3/*3 carriers were compared, or how this genetic variant influences fentanyl requirements for adequate analgesia is currently unknown. Whether competitive inhibition of cytochrome P450 3A5 is similar to 3A4 is also unknown; the potential differences have been suggested in a study showing that ketoconazole inhibited CYP3A4 more than it did CYP3A5 for midazolam metabolism[40].

No genetic polymorphism is currently described for CYP3A4. Its activity varies considerably; pro-inflammatory cytokines down regulate CYP450 enzyme content and activity in the animal model[41]. This same effect has been described in humans. Patients requiring critical care after undergoing elective aortic aneurysm repair or major general surgery patients were assessed with (technique for activity) as a surrogate for CYP 3A4 activity; Interleukin 6 (IL-6) was used as a surrogate marker for inflammation. Cytochromic activity initially increased over the 24 hours after the intervention, followed by a marked reduction over 72 hours [42]). Higher levels of IL-6 were associated with significantly lower cytochromic activity. When leukocyte counts and C reactive protein levels were used as inflammation markers in critically ill children, however, no relationship with midazolam metabolism

(inferred on the basis of midazolam requirements rather than levels, and presumed to be CYP 3A4 mediated) could be identified[43]. Midazolam clearance was assumed strictly on the basis of midazolam requirements and sedation levels. Sepsis-related encephalopathy [44, 45] may thus be at least in part related to inflammatory mediators and their direct physiological effects. However, if the patient is receiving sedatives or opiates metabolized by the cytochrome 3A4 pathway, drug metabolism and clearance may vary not only because of co-administered drugs but also because of variable levels in inflammatory mediators

The metabolism of sedatives and opiates by CYP450s

Fentanyl and midazolam are commonly administered in the critical care setting[46] and are extensively metabolized by the same CYP450 isoenzymes, namely, CYP3A4/5[47, 48]. Co-administration of FEN and MDZ, or of either, with other drugs metabolized by the CYP3A4/5 isoenzyme[32] increases serum drug levels by competitive inhibition; metabolism and excretion of these drugs decreases with age[49]. In vitro studies suggest that fentanyl competitively inhibits metabolism of midazolam using a human hepatic microsome and recombinant cytochrome P450 isoforms model. Fentanyl competitively inhibits metabolism of midazolam to l'-OH MDZ by CYP3A4 [50]. Propofol, another commonly used sedative, is metabolized by a different CYP450 (CYP2C19); its presence inhibits 2D6 function[51] and alters 2D6 substrates (such as haloperidol, codeine, oxycodone, and tramadol) and antipsychotic metabolism. However, its impact on CYP450 3A4/5 activity is believed to be mediated by metabolic inhibition; fentanyl and midazolam levels are increased through that mechanism[51].

We compared the biological and drug treatment characteristics in 100 patients who developed coma or delirium while receiving sedatives or opiate analgesics in ICU[39]. Coma was not associated with the fentanyl dose received prior to the occurrence of coma, but was associated with the co-administration of CYP3A inhibitors (r=0.31; p=0.005) and with fentanyl plasma levels (3.7 +/-4.7 vs. 2.0 +/-1.8 ηg/ml, p=0.0001), while delirium was not. Similarly, coma was not associated with midazolam doses administered prior to the occurrence of coma, but was associated with midazolam plasma levels (1050 +/-2232 vs. 168 +/-249 ηg/ml, p=0.0001), while delirium was not. These data suggest that iatrogenic coma in the critical care setting is at least partly attributable to cytochromic pathway drug-drug

interaction. In addition, the data suggest the mechanistic pathways leading to coma or to delirium may differ, and that cerebral dysfunction may not predictably be a disease spectrum of 'brain failure' as has been proposed.

The pharmacokinetics of midazolam (MDZ) are well characterized, and its pharmacodynamics are predictable in healthy adults [52]. Midazolam is exclusively metabolized by CYP3A4 and metabolic clearance in healthy populations is preserved over a relatively narrow range[53, 54].Information on the effect of critical illness, however, on the PK and PD of midazolam is less reported. Midazolam drug levels were sampled daily in nine septic critically ill patients and compared to otherwise stable outpatients receiving midazolam for procedural sedation. Plasma levels, half-life and terminal half-life varied within a considerably broader range than that reported in the literature to date, and in comparison to normal subjects[55] , with very broad intra and inter subject variability (tables 1 and 2, and figures 3 and 4, below). In addition, terminal half-life, which is determined after drug infusion cessation, was prolonged in all patients, and contrasted with previously published values in less ill populations. These characteristics are in keeping with description in a pediatric critical care population where lower midazolam elimination was observed in comparison to other studies in pediatric patients[56], and felt to be attributable, among others, to covariates such as renal failure, hepatic failure, and concomitant administration of CYP3A inhibitors.

Table 1: Midazolam Dosing Duration and Mean Concentration		
	Continuous infusion	Intermittent dosing*
Days	8.8	4.8
MDZ []	265 +/- 177	100 +/- 134

Table 1: *Bolus dosing in the same nine critically ill patients administered on an as needed basis following discontinuation of midazolam infusion; Concentrations are expressed in ηg/mL, and presented as mean +/- SD.

Table 2: Pharmacokinetic Parameters in Study Participants and Healthy Controls				
PK Parameter	Study Patients		Healthy Controls‡	
	Mean +/- SD	Range	Mean +/- SD	Range
CL_{ss} (mL/min)	418 +/- 324	31-1157	376	267-485
$T_{½}$ (h)	16.0 +/- 9.6	2.3-34.9	3.2	1.0-4.0

Table 2: comparison of midazolam clearance and half-life in the 9 septic ICU patients and four patients receiving MDZ for procedural outpatient interventions.

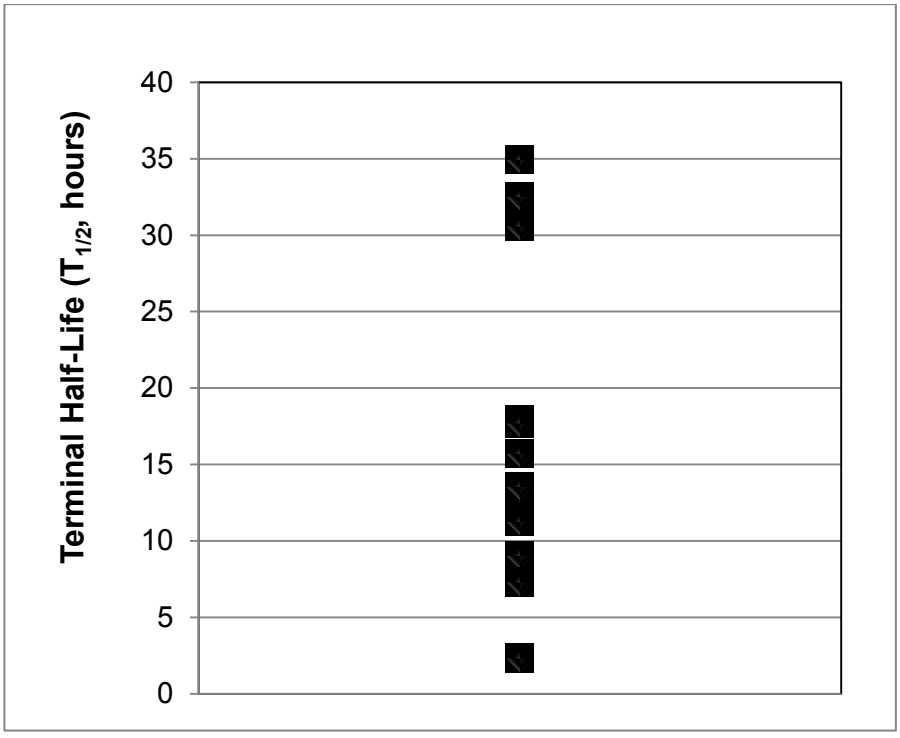

Figure 3: Variability in terminal half-life of midazolam among the nine septic ICU patients.

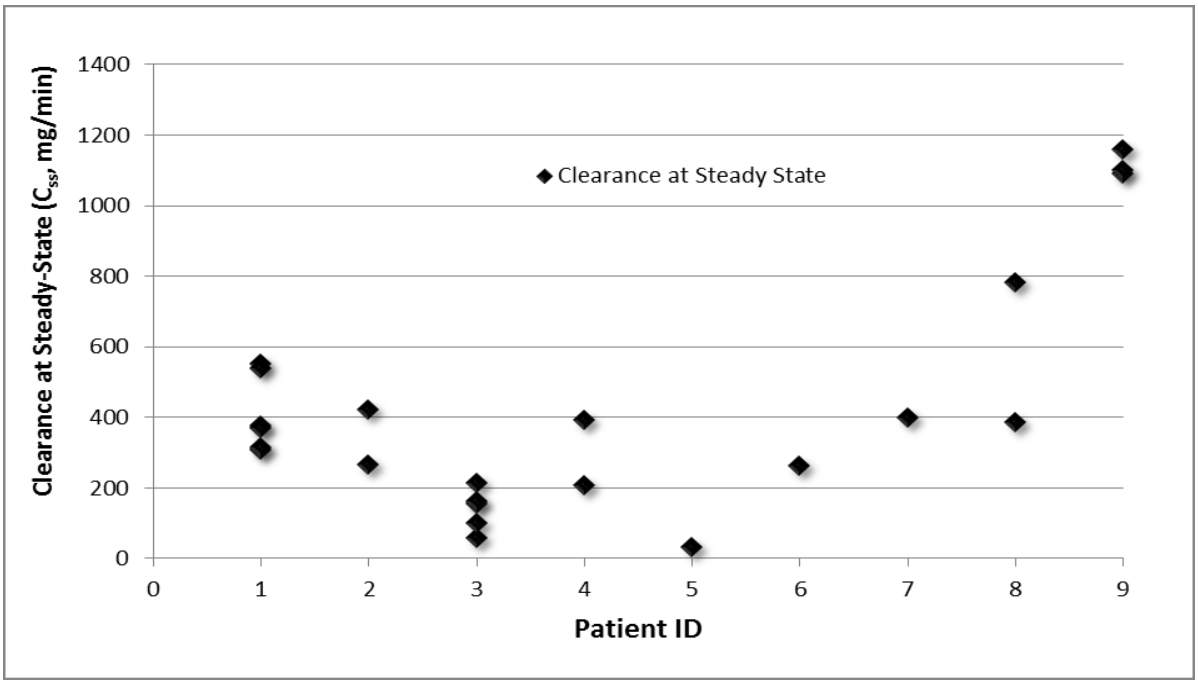

Figure 4: Observed intra- and intersubject variability in MDZ clearance at steady-state.

Disease and genotype associated drug metabolism alterations

The vulnerable critically ill metabolize sedatives differently than do healthy elective surgery patients [39, 56, 57]. This, in addition to drug-drug interactions, can lead to excessive sedation and elevated opiate and benzodiazepine levels[39]. Because renal dysfunction, hepatic abnormalities and drug-drug interactions are prevalent, particularly in older critically ill patients, analgesic and sedative pharmacokinetics may contribute to alterations in level of consciousness. Poorly defined entities such as septic encephalopathy may at least partly be attributable to inflammatory or other pharmacologically related, and therefore modifiable, effects.

While no CYP P450 3A4/5 genotypic variants have been shown to cause a phenotypic change in drug metabolism, various genotypes of the CYP 2D6 are associated with clear and clinically significant drug metabolism differences. Twenty percent (20%) of drugs are metabolized by cytochrome P450 2D6. Approximately 80 allele variations in CYP 2D6 have

been identified[58]; their impact on clinical outcomes is primarily linked to their effect on metabolism. Individuals with two non-functional alleles at 2D6 are considered poor metabolizers. O-demethylation of codeine by CYP 2A6 metabolism accounts for only 10% of the administered codeine's metabolism, but is essential in producing its active metabolite, morphine. The 7 to 10% of Caucasians with the poor metabolizer genotype cannot get analgesic effect from codeine because of their inability to produce morphine. Persons with one or two functional alleles are considered extensive metabolizers, and those with duplicate or amplified active CYP 2D6 are considered ultra-rapid metabolizers. A minority of North American or European Caucasians, but more than 25% of Ethiopians, for instance, have genetically determined ultra-rapid metabolism. Ultra-rapid metabolizers produce serum levels of morphine 20 to 80 fold higher than those produced by extensive metabolizers given the same codeine dose. The 2D6 pathway produces active metabolite but only accounts for a small proportion of drug disposal. N-demethylation of codeine, and its glucoronidation, account for 80% of the remaining metabolism[59]. N-demethylation is CYP 3A4 dependent.

The importance of understanding genetic variability, and active metabolite and elimination pathways, was elegantly illustrated in a case report describing an ultra-rapid metabolizer who received a moderate dose of codeine[9]. In the case featured in the New England Journal of Medicine, the featured patient received codeine while receiving voriconazole and clarithromycin, two CYP 3A4 inhibitors. The patient had concomitant renal failure. He became unconscious and developed hypercarbic respiratory failure, required mechanical ventilation, intensive care admission and a naloxone infusion. Genotyping and serum drug sampling confirmed very high serum morphine levels, induced by the ultra-rapid metabolizer profile, which were compounded by his inability to clear the morphine or morphine-3-gludorinide and morphine-6-glucorinide, morphine's neurotoxic metabolites, because of the co-administration of CYP 3A4 inhibitors and the concomitant renal failure. Since this publication, other cases of respiratory depression and death due to codeine administration in rapid metabolizers have been reported[60].

Whether utra-rapid CYP 2D6 metabolizers are at risk for other forms of toxicity than high serum morphine levels after codeine administration is not clear. One study seeking to link post-operative cognitive dysfunction (POCD) to cytochrome p450 polymorphism by genotyping of 2D6 and 2C19 in 337 patients showed no link between polymorphisms and POCD outcome [61]. The 2D6 ultra-rapid metabolizers had, however, by far the highest incidence of POCD, at 25% on first assessment, and with a two-fold incidence of POCD at both one week and three month post-operative testing in comparison to all other metabolizer profiles. This difference was not considered statistically significant on multivariate analysis, however, when age and type of surgery were considered.

P glycoprotein (P-gp)

P-glycoprotein is an efflux transporter with the capacity to extrude intracellular medication to the extracellular matrix; it exists on the apical surface of intestinal epithelial cells, in the biliary tree, in the kidney tubules and on the blood brain barrier [62-64]. P-glycoprotein (P-gP) limits xenobiotic absorption and acts as a protector against drug accumulation by promoting urinary and biliary xenobiotic efflux. Cerebral cells are protected by P-gP at the blood brain barrier (BBB0 level. P-glycoprotein is a key transporter for many therapeutic agents, among them fentanyl [65]. In a pilot cohort of 100 patients receiving fentanyl and midazolam, we measured P glycoprotein polymorphism to test whether it was associated with the occurrence of delirium or iatrogenic coma and found no correlation[39]. P glycoprotein inhibitor administration was, however, associated with the number of days patients were deemed delirious ($r=0.32$; $p=0.002$). Whether this effect had any relationship with cerebral accumulation of fentanyl, midazolam, or their potentially toxic metabolites was not tested as cerebrospinal fluid was not sampled in that study.

Pharmacokinetic variables

The response to acute physiologic stress, aggressive hemodynamic resuscitation and organ dysfunction significantly alter drug response in the critically ill and in a critically ill individual over time. One example of this effect is the wide variations in serum albumin attributable to alterations in liver synthesis and dilution. This may affect highly protein bound drugs such as propofol, midazolam and fentanyl. When in vitro plasma protein binding and

distribution in blood of fentanyl was studied in healthy human volunteers, in plasma, 84.4% of fentanyl was bound[66]. Propofol significantly raises the rate of albumin-unbound free midazolam in an in-vitro albumin model[67]. The effects of acute illness and protein shifts on midazolam and fentanyl bioavailability may thus vary with fluid resuscitation and protein synthesis by the liver.

Inflammation and neurotransmitters

The relationship between sepsis and cerebral dysfunction is explored elsewhere in this book. Several reports suggest a relationship between systemic inflammation and behavioural changes, some of which may be attributable to and blood brain barrier permeability. An increase in plasma levels of pro-inflammatory cytokines has been linked to delirium[68] and depression[69]. IL-1β injected into rat brains causes an increase in blood brain barrier permeability[70]. IL-8 is a potent neutrophil chemotactic agent; its expression may also act to increase blood brain barrier dysfunction[71].IL-6 is able to cause a substantial increase in the permeability of the BBB[72]. Chemokines have also been shown to modulate BBB permeability[73]. In one small human ICU study, an association was found with IL-8 levels and delirium[74] . Other reports identify variable drug transport across the blood brain barrier with accumulation of toxic metabolites in the brain. IL-6 influenced morphine metabolite transport across the BBB in critically ill patients[75], raising the possibility that it may also modulate the distribution of other drugs.

In a pilot cohort of 100 patients receiving fentanyl and midazolam studied to assess determinants of delirium or iatrogenic coma, delirious patients had higher levels of IL-6 than comatose patients (129.3 vs. 35.0 pg/ml, p=0.05), suggesting that the inflammatory mediator patterns may differ in various clinical presentations of alterations in consciousness combined with cognitive abnormalities, that some authors have termed ‘cerebral dysfunction’ to describe this spectrum in the critically ill.

The ICU environment is unique in that it contextually associates factors associated with critical illness with some of the mechanisms postulated to cause delirium [76, 77]. These include neurotransmitter imbalance, inflammation, blood brain barrier permeability, as well as abnormal levels of large neutral amino acids. Some amino acid precursors such as tryptophan

are believed, in the context of increased plasma concentrations, to influence both neurotransmitter levels and neuroinflammation [78]. Tryptophan competes with tyrosine and leucine for transport across the blood-brain barrier; increased cerebral uptake of tryptophan and phenylalanine leads to elevated levels of neurotransmitters such as serotonin and norepinephrine. Decreased ratio of tryptophan to other large amino acids has been associated with delirium. A recent study investigated the association between plasma kynurenine concentrations and kynurenine/tryptophan ratios, and acute brain dysfunction, defined as the presence of either delirium or coma [79]. Among the 84 patients studied, and after adjusting for age, sedation regimen and severity of illness, elevated kynurenine and kynurenine/tryptophan ratio were associated with fewer delirium/coma-free days, leading to speculation as to a biochemical mechanistic pathway. There were, however, limitations to the analysis. Assessment of the plasma kynurenine/tryptophan ratio (the most common tool in clinical investigations of tryptophan - kynurenine metabolism) does not distinguish between the activity of two rate-limiting enzymes of kynurenine formation from tryptophan: tryptophan 2, 3-dioxygenease (TDO) and indoleamine 2, 3 dioxygenase (IDO). Each enzyme activity is enhanced by other factors common in the critically ill: TDO by stress hormones (cortisol) and IDO by proinflammatory cytokines (tumor necrosis factor (TNF) -alpha and interferon-gamma)[80]. These enzymatic pathway activities have been studied in depression, and are suspected to play an important role in psychosis and cognition[80]. The rate of kynurenine metabolism, or changes associated with the ability of kynurenine metabolites to penetrate the central nervous system, cannot be differentiated given the challenges of measuring the direct metabolites of kynurenine (e.g. kynurenic acid). In addition, a single plasma kynurenine and tryptophan measurement as described in the study would not capture the association between changes in the kynurenine/tryptophan ratio over time and delirium, coma, or both, or account for the fluctuating nature of both delirium and coma during the ICU stay. Moreover, the validity of combining delirium and coma as a single outcome is the subject of some debate since no biologic rationale supports an association between the kynurenine pathway with unresponsiveness, in addition to recent data suggesting that iatrogenic coma and delirium in the ICU are not mechanistically-linked[39].

Conclusion

Some authors deplore the lack of timely of timely transmission of pharmacogenomic interactions into clinical practice[81] , and the relative paucity of prospectively validated genetic risk data on the vulnerable and expensive critically ill population[82] . That drug-drug interactions and genomic variations impact on level of consciousness appears clear from data in critically ill adult and pediatric populations to date. Delirium and its association to sedatives and analgesics present several challenges. Screening tool inconsistencies and potential confounding by sedation, in addition to the pharmacologic findings described above, make the association between benzodiazepines and delirium less convincing[83]. Overall, drug interactions in the critically ill are probably common and may be harmful; identifying the most significant ones, identifying their clinical impact and raising the awareness of the critical care community is a scientific and educational challenge.

Should Benzodiazepines be avoided in mechanically ventilated patients?

No.

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The preoccupation that critically ill patients should be free from pain, agitation, and anxiety while in intensive care motivates physicians to prescribe analgesics and sedatives. Benzodiazepines are part of what is meant to be pharmacological optimization of patient comfort. How much sedation should be used, and for how long, has recently become the focus of scientific debate. At the heart of this deliberation is the conviction by many caregivers that sedation mitigates how traumatic the patient perceives the ICU experience to be. This notion is slowly being contradicted by data from follow-up studies [1]. In contrast, there is an emerging understanding that excessive sedation, with its short or medium term decreases in consciousness, is common, and is associated with increased morbidity, mortality, and expenditure[2, 3]. It is important to differentiate outcomes associated with excess sedation, which is harmful, from benzodiazepine use, which is not.

No benzodiazepine has all the ideal characteristics one would wish for in a sedative, such as rapid onset, rapid recovery, a predictable dose response, a lack of drug accumulation, and an absence of toxicity. All benzodiazepines do share one desirable characteristic: they are inexpensive. The pharmacokinetic, pharmacodynamic, and pharmacogenetic effects inherent to this drug class are helpful in understanding their administration, and to the clinician's interpretation of the data available in current sedation studies.

The ɣ-aminobutyric acid A ($GABA_A$) cerebral neuronal receptor activation inherent to benzodiazepine activity is part and parcel of their anxiolytic, amnesic, sedating, hypnotic, and anticonvulsant effects[4] . Sensitivity to benzodiazepine effect increases with age, and benzodiazepine clearance decreases in the elderly[5]. Respiratory depression and systemic hypotension can occur when benzodiazepines are administered with other drugs, especially opioids, in patients with cardiovascular instability or respiratory failure but these side effects compare favorably with those associated with other sedatives. All benzodiazepines are

metabolized by the liver. Benzodiazepine clearance is reduced in patients with hepatic dysfunction[6]. Delayed emergence from sedation with benzodiazepines when benzodiazepines are administered continuously can be associated with advanced age, hepatic dysfunction, or renal insufficiency[7].

Choice of benzodiazepine matters in understanding its effects on individual patients, particularly when it comes to decreasing intermittent or continuous doses, or increasing administration intervals. Lorazepam's effect and elimination time are increased in patients with renal failure[4] . Midazolam and diazepam's active metabolites accumulate with prolonged administration, an effect heightened by renal dysfunction [8] . Diazepam saturates peripheral tissues, and its active metabolites can accumulate in patients with renal insufficiency, lengthening clinical effect duration[9]. Comparative studies of prolonged use of midazolam and lorazepam in ICU patients suggest greater variability and longer time to awakening with midazolam than with lorazepam[6, 10] .

The response to acute physiologic stress, aggressive hemodynamic resuscitation and organ dysfunction also alter drug response in the critically ill and in a critically ill individual over time. One example of this effect is the wide variations in serum albumin attributable to alterations in liver synthesis and dilution. This may affect highly protein bound drugs, such as midazolam. The effects of acute illness and protein shifts on midazolam bioavailability may thus vary with fluid resuscitation and with variability in protein synthesis by the liver. The pharmacokinetics of midazolam were thought to be well characterized, with predictable pharmacodynamics in healthy adults. However, a recent study describing midazolam drug levels, half-life and terminal half-life in nine septic critically ill patients suggested considerable variability within a much broader range than has been reported in the literature to date, and in comparison to normal subjects[11] , with significant intra and inter subject variability. In addition, terminal half-life, which is determined after drug infusion cessation, was prolonged in all nine septic patients, and contrasted with previously published values in less ill populations. These characteristics are in keeping with description in a pediatric critical care population where lower midazolam elimination was observed in comparison to other studies in pediatric patients[12], and felt to be attributable, among others, to covariates such as renal failure, hepatic failure, and concomitant administration of CYP3A inhibitors.

Medications that inhibit either cytochrome P_{450} enzyme systems and/or glucuronide conjugation in the liver affect the clinical effect of benzodiazepines. The cytochrome P 450 3A4/5 pathway is shared by more than half of the medications administered in an ICU. Fentanyl and midazolam, for instance, are commonly co-administered in critical care and are extensively metabolized by the same CYP450 isoenzymes, namely, CYP3A4/5[13]. Further, genetic polymorphisms are associated with the functional level of expression of these enzymes (especially CYP3A5)[14] which may also predispose patients to highly variable central nervous system effects of midazolam. Excessive sedation can occur during co-administration of these drugs due to competitive inhibition and increased serum or tissue drug levels. Co-administration of fentanyl and midazolam[15], of midazolam and voriconazole[16], and of midazolam and fluconazole[17], predictably increase midazolam blood levels and midazolam clinical effect.

Benzodiazepine-based continuous sedation has been associated with prolonged dependence on mechanical ventilation, and increased ICU LOS[18, 19] in some studies, and not in others[20, 21]. No study accounted for patient age, renal or hepatic dysfunction, or other pharmacokinetic, pharmacogenetic or drug-drug interactions to better illuminate whether these differences may have accounted for the discordant findings. More recent sedation trials are describing study entry and study duration sedation levels; additional data on sedation assessments after benzodiazepines and other drugs have been discontinued would also illuminate the relevant variables, because of the half-life and metabolite variables mentioned above. Large differences in sedation practice have been highlighted with these sedation trial publications of baseline data; some trials[22], such as the 'Awakening and Breathing' Controlled trial, entered patients whose average sedation level (measured by the Richmond Agitation and Sedation Scale) suggested they were only responsive to pain (RASS levels of -4), whereas other sedation and analgesia titration trials describe patients sedated quite lightly at baseline[23] (RASS levels of -0.4). Considering these elements at study entry and over time are important when reviewing publications; the risk or benefit of a given intervention may be associated with choice of molecule or level of sedation, and both variables should be available to the reader. If one of the molecules is a benzodiazepine, factors influencing its effect and duration should also be reported.

Several publications suggest an association between the dose of continuously administered benzodiazepine and delirium in critically ill patients[24, 25]. Because continuously sedating patients with midazolam appears associated with a higher incidence of delirium than sedating patients with dexmedetomidine[26], and because this difference is not seen when morphine is compared to dexmedetomidine[27] midazolam has been presumed to be linked to delirium occurrence. The Confusion Assessment Method (CAM-ICU) screening tool was the tool used to detect ICU delirium in the studies describing less delirium with dexmedetomidine, a molecule is associated with greater wakefulness than midazolam. Some authors have suggested that the CAM-ICU scoring may be affected by sedation[28]; the potential that the greater sedation seen and expected with midazolam was a confounder for delirium remains to be clarified before convincing conclusions can be drawn. The therapeutic effect of dexmedetomidine in delirium, currently under study, remains to be proven.

The importance of avoiding excessive sedation has been emphasized in recent years in publications suggesting that daily interruption of sedative infusions, titration of sedative dose and opiates to symptoms[29, 30], and minimization of drug administration is associated with patient benefit, reduced costs[31] and does not lead to accidental device removal or psychological stress. No study has convincingly made the point that type of drug makes a difference, with the caveat that studies to date have been limited to in-hospital events and not long-term comparisons between drug classes and doses. Benzodiazepines are inexpensive, safe, and familiar to clinicians and readily adjusted to patient symptoms. Titration, and particularly adjusting and reducing, as needed, sedative doses to achieve the desired effect, is beneficial. Rigorous avoidance of iatrogenic (sedative-induced and inadvertent) coma is key; it reduces costs, duration of mechanical ventilation, and the incidence of sub-syndromal delirium[23, 32], a state between cognitive normalcy and full-blown delirium[32] detectable with the Intensive care delirium screening checklist tool. Benzodiazepines can be adjusted in this manner, and remain the most affordable sedative, a relevant dimension of our choices in pharmaceuticals[33] . The benefit of more expensive alternatives has yet to be shown in sedating- lightly and only as needed- the general critical care population.

Discussion/response (counterpoint): Excessive sedation is harmful; Drs Girard, Dittus, Ely and I agree. Much of what is administered in terms of sedation by caregivers aims

to relieve suffering, from a position of authority and decision-making. In the critically ill patient, the temptation to maintain deep sedation aims to avoid movement, hoping that complications such as self-extubation may be avoided[34], when in fact no association exists between wakefulness and removal of catheters or devices[29]. The concern that the patient may be experiencing discomfort should indeed be followed by an assessment as to the origin of the discomfort rather than by an effort to mask it. This requires a certain degree of stoicism, as well as the skills and interest in identifying the source of the patient's distress. It is apparent that overly sedated patients do not recover quickly or well. While excess sedation is harmful, benzodiazepine use is not.

My colleagues from Vanderbilt believe that benzodiazepines harm patients. This perspective is highlighted by statements such as '*benzodiazepines to sedate patients in the ICU is a hallmark component of an antiquated and dangerous way…*'; '*benzodiazepines must be discarded as a sedative*'; '*propofol has nearly uniformly been found superior to the benzodiazepines'; 'Primum non nocere.. is a key feature of the Hippocratic Oath*'. With the exception of the Hippocratic Oath content, little support can be found to justify for my colleagues' arguments. When a molecule is readily available in many forms, has been used for decades and has clinical benefits, pharmacokinetic properties and side effects that are well understood, and is the least expensive sedative available on the market, it behooves the critical care clinician to consider its use. If benzodiazepines are used in studies describing lorazepam infusions or intermittent lorazepam administration in critically ill patients that do not take into account the half-life of lorazepam and its comparator drugs, such as dexmedetomidine or propofol, what should one conclude? Clearly, addressing the drug's pharmacokinetic characteristics is preferable to stating that lorazepam is a poor choice of medication[35]. If two characteristics- wakefulness and greater sedation- characterize two molecules- for instance wakeful sedation with dexmedetomidine and more somnolent sedative effect with lorazepam, and if the more sedating benzodiazepines are predictably associated with more somnolence, which may be misinterpreted as being delirium[28], this does not make the choice of benzodiazepines an antiquated or a dangerous one. Thoughtfulness and knowledge- here particularly with regard to pharmacokinetics and drug interactions- can make a clinician

choose a molecule such as a benzodiazepine, assuming a thorough understanding of its effects and metabolism.

Two straightforward motivations to choose a benzodiazepine come to mind. The first is patient preference. Some patients explicitly prefer being more sedated, whereas others prefer being more awake. In my clinical experience, the division is roughly 50/50 (with 50% of patients preferring a sleepier state, and preferring amnesia). Several of these patients already consume benzodiazepines and find them therapeutically useful. The second reason is drug cost. Critical care and critical care pharmacy costs account for a large percentage of what is spent in a hospital; benzodiazepines are inexpensive, and recent large trials with more expensive drugs as comparators such as MIDEX and PRODEX[36] do not appear to justify unequivocally choosing the more expensive molecules[33].

Benzodiazepines have been shown to be useful in alcohol withdrawal or status epilepticus, albeit with poor evidence to endorse them for these indications in ICU patients. Although I do not use benzodiazepines in all ICU patients, they remain part of my therapeutic armamentarium; they offer an interesting alternative both because of their benefits and lesser expenditure.