2. Les anti-émétiques

Ces dernières années, l'évolution a été marquée par le developpement du NEPA (association en 1 seul comprimé oral de nétupitant et palonosetron) et l'importance croissante de l'olanzapine.

- **Les antagonistes des récepteurs à la sérotonine de type 3 (anti-5-HT3) ou sétrons :**
  Trois substances actives sont commercialisées en France :
  - Deux de première génération : Ondansétron et Granisétron.
  - Le palonosétron : molécule de seconde génération, recommandée comme alternative préférentielle aux sétrons de 1ère génération pour les chimiothérapies moyennement et hautement émétisantes (par voie intraveineuse, 30 minutes avant le début de la chimiothérapie émétisante et à la dose de 250 µg). Une alternative orale (0.5mg) semble équivalente (12).
  Une forme de granisetron longue-durée par voie sous cutanée a montré son équivalence par rapport au palonosetron IV (13). En revanche, une méta-analyse étudiant le granisetron sous la forme sous-cutanée versus sa voie orale démontre une supériorité de la prise orale dans le contrôle des NVCI (14).
  Effets secondaires les plus fréquents : céphalées, constipation et élévation transitoire des transaminases. Les sétrons sont déconseillés en association avec certains Inhibiteurs des Tyrosines Kinases en raison d'un risque d'allongement du QT (Voir tableau 6).

- **Les corticoïdes :**
  Bien que leur efficacité soit démontrée depuis longtemps, leur mode d'action reste mal connu. La molécule la plus étudiée, dans la littérature, est la dexaméthasone. Toutefois, aucune preuve ne pourrait laisser penser que l'efficacité soit différente selon le type d'agent utilisé.
  Une méta-analyse sur données individuelles (5 études, 1194 patients) a retrouvé une non-infériorité de la prise unique au jour 1 de dexaméthasone associée au palonosetron par rapport à la prise prolongée sur 3 jours des 2 molécules (15). De plus, il n'y a pas de preuve clinique justifiant le retrait de la corticothérapie lorsqu'une molécule d'immunothérapie est utilisée en combinaison à la chimiothérapie (16).
  Le tableau 3 reprend, pour mémoire, les équivalences de doses des corticoïdes (17).

Molécule	Activité anti-inflammatoire	Eq. Dose
Hydrocortisone	1	20 mg
Prednisone Prednisolone	4	5 mg
Méthylprednisolone	5	4 mg
Dexa et béta-méthasone	25-30	0,75 mg

Tableau 4 – Equivalences d'effet et de dose des différents glucocorticoïdes

- **Les antagonistes des récepteurs aux neurokinines de type 1 (Anti NK1) :**
  L'aprépitant (Emend®) par voie orale est la seule molécule de cette classe disponible en France. Associé aux autres anti-émétiques, il améliore significativement le contrôle des NVCI en phase aiguë et retardée notamment pour les chimiothérapies hautement émétisante (18).
  Effets secondaires les plus fréquents : troubles digestifs (constipation, diarrhée, dyspepsie, éructations), asthénie, anorexie et hoquet.
  L'aprépitant est un inhibiteur du cytochrome P450 3A4. Cet agent est à ce titre pourvoyeur de plusieurs interactions médicamenteuses. Parmi celles-ci on retiendra notamment (19) :

- Les interactions avec les **corticoïdes** :
  - La dose orale habituelle de dexaméthasone doit être réduite d'environ 50% en cas de co-administration avec l'aprépitant selon le schéma posologique de 125 mg/80 mg.
  - La dose habituelle de méthylprednisolone administrée par voie intraveineuse doit être réduite d'environ 25 %, et la dose orale habituelle de méthylprednisolone d'environ 50 % en cas de co-administration avec l'aprépitant selon le schéma posologique de 125 mg/80 mg.
- Les interactions avec la **warfarine**: risque de diminution de l'INR.
- Les interactions avec les **contraceptifs à base d'éthinyloestradiol et de noréthindrone** : diminution de leur efficacité.

- **Formes combinées (Anti-NK1 + 5HT3)**

  Le NEPA (association fixe orale de nétupitant 300 mg et palonosetron 0.5 mg), s'administre 1 heure avant la chimiothérapie par cisplatine au J1 uniquement. L'efficacité de cette molécule combinée à la dexaméthasone est non-inférieure au triplet habituel (aprépitant + granisetron + dexaméthasone) (20,21). L'association est commercialisée en France sous le nom d'AKYNZEO® et remboursée dans l'indication suivante : « traitement de 1ère intention en prévention des nausées et vomissements aigus et retardés associés aux chimiothérapies anticancéreuses hautement émétisantes à base de cisplatine ». Un avis défavorable à son remboursement pour les prescriptions dans les chimiothérapies moyennement émétisantes a été émis en décembre 2020 par la commission de transparence de l'HAS (SMR insuffisant). Ce médicament est néanmoins proposé par l'ASCO dans ses dernières recommandations de 2017 et par la MASCC/ESMO en 2016, en prévention des NVCI pour les chimiothérapies moyennement émétisantes contenant du carboplatine.

  Par ailleurs, une étude coût-efficacité comparant l'aprépitant + granisétron versus le NEPA est en faveur du NEPA (22).

- **Les antagonistes des récepteurs à la dopamine 2 (Anti D2) :**

  Il s'agit de la classe médicamenteuse la plus anciennement utilisée mais également celle avec l'index thérapeutique le plus faible.

  Les molécules disponibles sont le métoclopramide, la metopimazine et l'alizapride.

  La domperidone a été inscrite sur la liste des médicaments sous surveillance renforcée de l'ANSM en 2014 en raison de l'observation d'effets indésirables graves cardiaques (dont allongement de l'intervalle QT et mort subite)[D]. L'AFSOS recommande de ne pas utiliser la Dompéridone.

  De même, l'EMA (*European Medicine Agency*) a émis une recommandation à propos du métoclopramide en raison de ses effets neurologiques[E]. Chez l'adulte, l'EMA recommande de ne pas dépasser la dose de 30 mg/j (3x10 mg) per os pendant 5j. Toutefois, les auteurs des recommandations MASCC/ESMO suggèrent, malgré cela, une utilisation possible jusque à des doses plus élevées pendant 2 à 3 jours.

- **L'olanzapine (Zyprexa®)**

  C'est un antipsychotique qui dispose d'un effet inhibiteur sur plusieurs récepteurs de neurotransmetteurs. Elle peut être utilisée dans la prévention et le traitement des NVCI aiguës et retardées. Après 4 études de phases III publiées de puissance insuffisante (23), unenouvelle étude de phase III (contre placebo) parue en 2016 montre, en association avec un traitement anti-nauséeux conventionnel, une réduction significative de

[D] Site de l'ANSM. De nouvelles recommandations pour minimiser les risques cardiaques des médicaments contenant de la domperidone - Point d'Information. 01/09/2014. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/De-nouvelles-recommandations-pour-minimiser-les-risques-cardiaques-des-medicaments-contenant-de-la-domperidone-Point-d-Information

[E] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Metoclopramide-containing_medicines/human_referral_000349.jsp&mid=WC0b01ac05805c516f

la fréquence des NVCI chez des patients recevant des chimiothérapies hautement émétisantes tant en phase aigue (74% vs. 45%, P=0.002) que retardée (<3j : 42% vs. 25%, P=0.002) (24). La posologie de 5 mg/jour a une efficacité similaire à celle utilisée intialement (10 mg par jour) avec moins de somnolence (18,19). Le surcoût est par ailleurs modeste. Les résultats de l'étude J-Force présentée en 2019 à l'ASCO (essai de phase III randomisé, contre *placebo*, évaluant l'efficacité de l'olanzapine à 5 mg ajouté au triplet sétron, corticoide et inhibiteur de NK-1) chez des patients recevant du cisplatine à plus de 50 mg/m² ont montré une amélioration de plus de 13% du contrôle complet en phase aigue et retardée avec une excellente tolérance[F]. Une revue systématique et méta-analyse publiée en 2019 (ESMO Open) regroupant 11 études randominées soit 1107 patients recevant une chimiothérapie hautement à moyennement émétisante (dont 561 dans le groupe olanzapine), démontre que l'ajout de l'olanzapine à 5 ou 10 mg versus sétron plus dexamethasone seuls diminue les NVCI notamment les grades III et IV ; la posologie de 5 mg est moins pourvoyeuse de somnolence et l'efficacité des 2 posologies sur la diminution des NVCI aigus et retardés est comparable (25). Dans les dernières recommandations de l'ASCO, l'olanzapine est associée systématiquement de J1à J4 dans la prévention des NVCI en cas de chimiothérapie hautement émétisante (26). Dans les recommandations MASCC/ESMO, qui n'ont pas été actualisées depuis 2016, ainsi que dans celles de l'AFSOS actualisées en 2017[G], l'olanzapine reste une option (27).

- **Les autres anti-émétiques :**
  -Le niveau d'efficacité des cannabinoïdes (marijuana à usage médical) ne permet pas de les recommander dans le traitement préventif des nausées/vomissements. Leur intérêt est néanmoins croissant (10,28). On rappelle qu'ils ne sont pas autorisés en France dans cette indication.
  -Le Lorazepam est un adjuvant utile mais ne doit pas être utilisé seul.

- **Régles hygiéno-diététiques (cf. référentiel AFSOS[G]) :**
  -Favoriser l'hydratation
  -Fractionner l'alimentation : 6 à 8 petits repas/collations /jour
  -Privilégier des petits repas froids, éviter les aliments gras/frits/épicés
  -Manger lentement
  -Boissons selon les goûts du patient entre les repas (eau, infusion, jus de pomme, coca), si besoin avec une tasse fermée et une paille (limitation des odeurs)
  -Maintenir une position assise 30 minutes après les repas (à défaut, en décubitus latéral droit)

- **Médecines complémentaires :**
  Il n'y a pas d'évidence en faveur ou défaveur des traitements dits complémentaires.
  L'acupuncture, en complément d'une prophylaxie médicamenteuse bien conduite, pourrait être efficace sur les nausées aigues sur la base de quelques essais randomisés de petites tailles (29). D'autres essais de plus grande ampleur sont en cours (30–32).

3. Prévention et prise en charge des NVCI

La prévention et le traitement des NVCI sont repris dans les tableaux 5 (chimiothérapies cytotoxiques & immunothérapie) et 6 (thérapies ciblées orales), adaptés des recommandations 2016 du du MASCC/ESMO (27,33) et 2017 de l'ASCO (26,34,35).

[F] Hashimoto H, Abe M, Nakao M, Mizutani H, Sakata Y, Fujita Y, Nishimura T, Hirano K, Okada H, Inui N, Sakata Y, Iihara H, Zenda S, Uchitomi Y, Yamaguchi T, Hoshina Y, Yanai T, Iwasa S, Yamamoto N, Ohe Y. A randomized, double-blind, placebo-controlled phase III trial evaluating olanzapine 5 mg combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based chemotherapy: J-FORCE Study. ASCO 2019, #11503

[G] AFSOS, Prise En Charge Des Nausées-Vomissements Chimio-Induits, MAJ 15/12/2017, disponible sur http://www.afsos.org/fiche-referentiel/nausees-vomissements-chimio-induits, accédé le 08/11/2019

Les différents types de chimiothérapies utilisées dans le traitement des CBNPC sont classés en quatre catégories en fonction de leur risque émétogène : hautement, moyennement, faiblement et minimal (36). Pour chacun de ces risques, un protocole de prévention et de traitement précis est recommandé. Dans les protocoles utilisant plusieurs drogues, il est nécessaire de tenir compte du niveau de la drogue la plus émétisante.
Il faut aussi adapter d'emblée le protocole en fonction des facteurs de risque éventuels du patient ; c'est la notion de « **prophylaxie surclassée** » si besoin dès la 1ère cure.

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