Au-delà de l'addiction : les multiples facettes des complications cliniques liées aux substances psychoactives

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addictovigilance.fr
le site de l'association française des centres d'addictovigilance

Contexte

- Les substances psychoactives à risque abus/addictif ont toutes un tropisme central…mais pas que
- Les complications psychiatriques, addictives, cognitives sont les plus connues, les plus fréquentes…mais ce ne sont pas les seules
- Les complications infectieuses (septicémie, endocardites, abcès…) souvent sévères sont également bien décrites, liées à la pratique d'administration et au terrain

- Les autres sont beaucoup moins connues, avec le risque de passer à coté…..

→ Exemples

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Complications neurologiques du Protoxyde d'azote

Tableau neurologique périphérique

- **Tableau d'atteinte du système nerveux périphérique assez stéréotypé :**

- Déficit moteur symétrique des membres inférieurs, à prédominance distale (steppage) → perte de la marche

-Troubles sensitifs sévères des 4 extrémités

-Ataxie proprioceptive marquée

-Présentation initiale sévère et subaigue souvent en quelques jours = Diagnostic différentiel avec un syndrome de **Guillain Barré syndrome**

- Peu de symptôme précessifs (parfois des paresthésie) : arrivée brutale des symptomes

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european journal of neurology

ORIGINAL ARTICLE

How to distinguish Guillain-Barré syndrome from nitrous oxide-induced neuropathy: A 2-year, multicentric, retrospective study

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Abstract

Background: Recreational use of nitrous oxide (N_2O) has dramatically increased in recent years, resulting in numerous cases of acute sensorimotor tetraparesis secondary to nitrous oxide-induced neuropathy (N_2On). Challenging clinical features can mimic Guillain-Barré syndrome (GBS), the main differential diagnosis upon admission. The most sensitive biomarkers for distinguishing between these two conditions remain to be determined.

Methods: Fifty-eight N_2On patients from three referral centers were retrospectively included over a 2-year period and compared to GBS patients hospitalized during the same timeframe (47 patients). Collected demographic, clinical, biological, and electrophysiological data were compared between the two groups.

Results: The typical N_2On clinical pattern included distal sensorimotor deficit in lower limbs with absent reflexes, proprioceptive ataxia, and no cranial involvement (56.7% of our cohort). Misleading GBS-like presentations were found in 14 N_2On patients (24.1%), and 13 patients (22.4%) did not report N_2O use during initial interview. Only half the N_2On patients presented with reduced vitamin B12 serum levels upon admission. A slightly increased cut-off (<200 pmol/L) demonstrated 85.1% sensitivity and 84.5% specificity in distinguishing N_2On from GBS. Only 6.9% of N_2On patients met the criteria for primary demyelination ($p < 0.01$), with only one presenting conduction blocks. A diagnostic algorithm combining these two biomarkers successfully classified all GBS-like N_2On patients.

Conclusions: Vitamin B12 serum level< 200 pmol/L cut-off and conduction blocks in initial electrophysiological study are the two most sensitive biomarkers for rapidly distinguishing N_2On from GBS patients. These two parameters are particularly useful in clinically atypical N_2On with GBS-like presentation.

KEYWORDS
Guillain-Barré, N_2O, neuropathy, nitrous oxide, toxic

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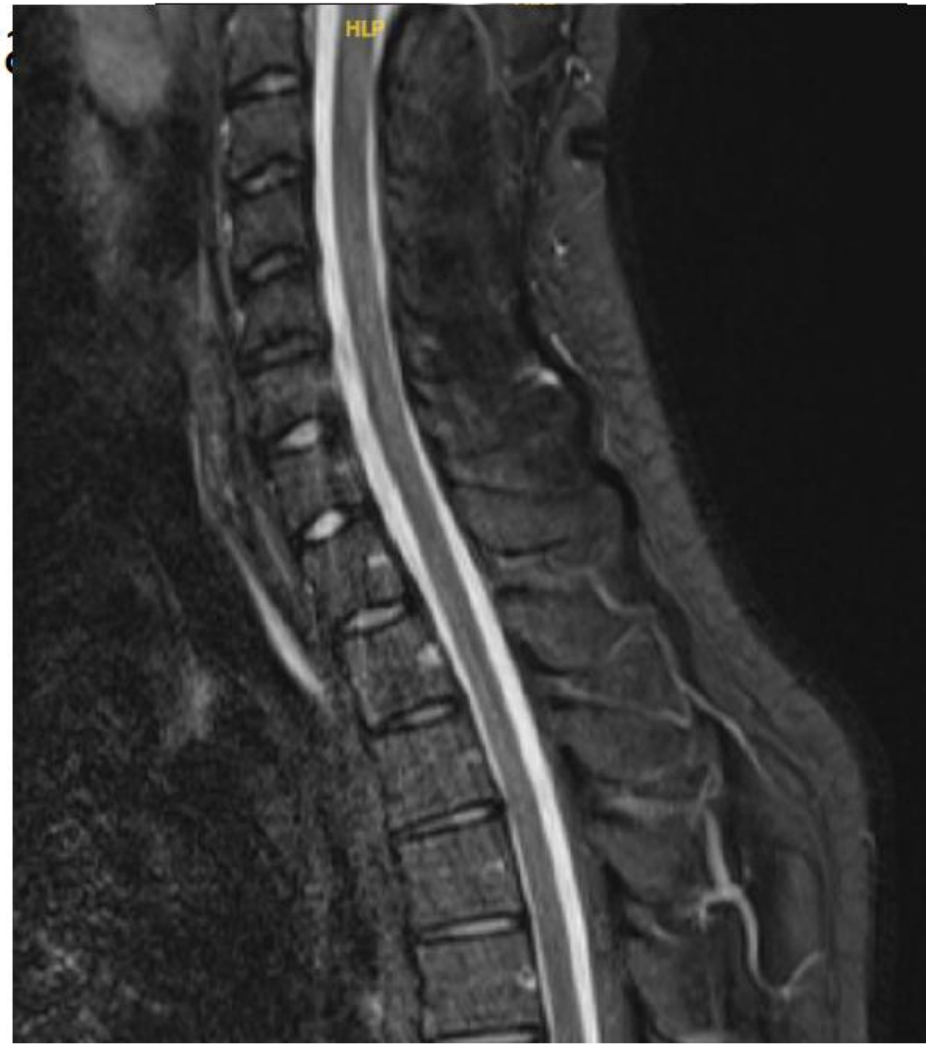
Tableau neurologique centra

- **Myélite cervicale** étendue à prédominance postérieure

→ Tableau d'ataxie sévère en 1er lieu

- Bonne récuperation clinique de l'atteinte centrale
- Les IRM de suivi montrent une disparition des lésions médullaires

- Pas de lésion cérébrale



Implications des services de rééducation fonctionnelle

Disabil Rehabil. 2025 Mar;47(5):1204-1213. doi: 10.1080/09638288.2024.2365987. Epub 2024 Jul 1.

Multidisciplinary rehabilitation following recreational nitrous oxide (N_2O) misuse: evaluating service provision and rehabilitation outcomes in a cohort with serious disability

Hannah Ryder [1 2], Simon Mosalski [1 2 3], Valerie Bramah [1], Robert Page [2 4], Steven G Faux [1 2 3], Christine T Shiner [1 2]

Affiliations + expand

PMID: 38950561 DOI: 10.1080/09638288.2024.2365987

Abstract

Purpose: Recreational nitrous oxide (N_2O) misuse is increasing globally. Chronic misuse can cause neurological impairments that require rehabilitation, though literature characterising rehabilitation is limited. This study aimed to evaluate rehabilitation service provision for impairments resulting from N_2O misuse.

Methods: A retrospective audit of hospitalised patients referred for rehabilitation for N_2O toxicity was conducted between 2015 and 2022 at a single metropolitan hospital. Data were collected *via* medical record audit and analysed via descriptive and non-parametric statistics.

Results: 16 eligible cases were identified, aged 18-43 years (50% female/male), with increasing case frequency. 12 cases received inpatient rehabilitation episodes for multifactorial sensorimotor, cognitive and psychosocial impairments. Cases articulated diverse rehabilitation goals and received intervention from a median of 6 clinical disciplines. All cases required assistance to mobilise or perform self-care activities on admission. Functional Independence Measure (FIM) scores significantly improved with rehabilitation (median FIM 84[75-93] to 117[112-123], $p < .001$). Despite gains in independence, all cases required referral for ongoing rehabilitation post-discharge.

Conclusions: Demand for inpatient rehabilitation for disabling N_2O toxicity appears to be increasing. In this series, cases were young, exhibited serious impairments, and had multidisciplinary rehabilitation needs. Inpatient rehabilitation led to significant functional improvements, though ongoing disability was evident post-discharge.

Keywords: Rehabilitation; disability; inhalant misuse; myeloneuropathy; nitrous oxide; spinal cord dysfunction; substance use; vitamin B12 deficiency.

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Systèmes

Effets vasculaires du proto :

Embolie Pulmonaire, Thrombose Veineuse profonde, Thrombose veineuse cérébrale

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CASE REPORT

Pulmonary embolism and deep vein thrombosis caused by nitrous oxide abuse: A case report

Wen Sun, Ji-Ping Liao, Yan Hu, Wei Zhang, Jing Ma, Guang-Fa Wang

Cerebrovascular Diseases

Stroke Spectrum

Cerebrovasc Dis
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Published online: September 7, 2021

Extensive Cerebral Venous Thrombosis Secondary to Recreational Nitrous Oxide Abuse

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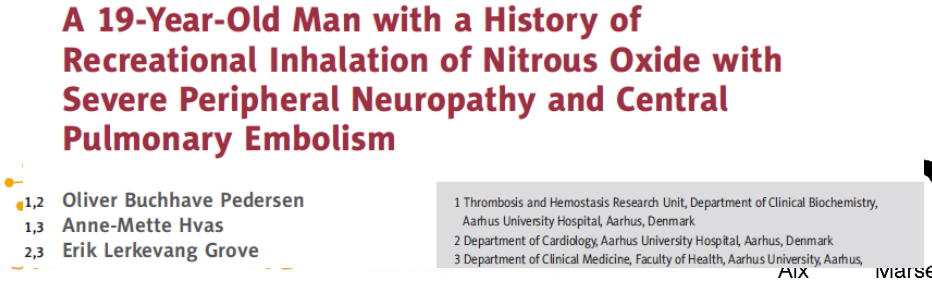

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DOI: 10.12659/AJCR.931936

A 19-Year-Old Man with a History of Recreational Inhalation of Nitrous Oxide with Severe Peripheral Neuropathy and Central Pulmonary Embolism

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Hyperhomocysteinémie

facteur de risque vasculaire

Aix Marseille Université

Institut de Neurosciences des Systèmes

Devant une thrombose veineuse cérébrale

Cerebrovascular Diseases

Stroke Spectrum

Cerebrovasc Dis
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Extensive Cerebral Venous Thrombosis Secondary to Recreational Nitrous Oxide Abuse

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The extensive workup for thrombophilia showed vitamin B12 deficiency (93 ng/L [N: 187–883 ng/L]), normal folate levels, and a 10-fold increase in the homocysteine level (134 µmol/L [N: <13.6 µmol/L]). Protein C, protein S, and antithrombin III levels were normal. No mutations for the factor V Leiden and MTHFR genes were found. Antiphospholipid antibodies and viral serologies for HIV, HBV, HCV, Lyme, and syphilis were all negative, and there were no arguments for disseminated intravascular coagulation.

Fille de 16 ans : céphalées, léthargie, nausées, vomissements depuis quelques jours. Hospitalisée en mai 2020.
Elle a été confinée durant 6 semaines (pandémie SARS Cov2) pendant lequel elle rapporte un usage quotidien de N20

- Bilan étiologique complet (thrombophilie, infectieux,...introduction récente de pilule OP) **négatif**
- Penser également à rechercher une consommation de protoxyde d'azote

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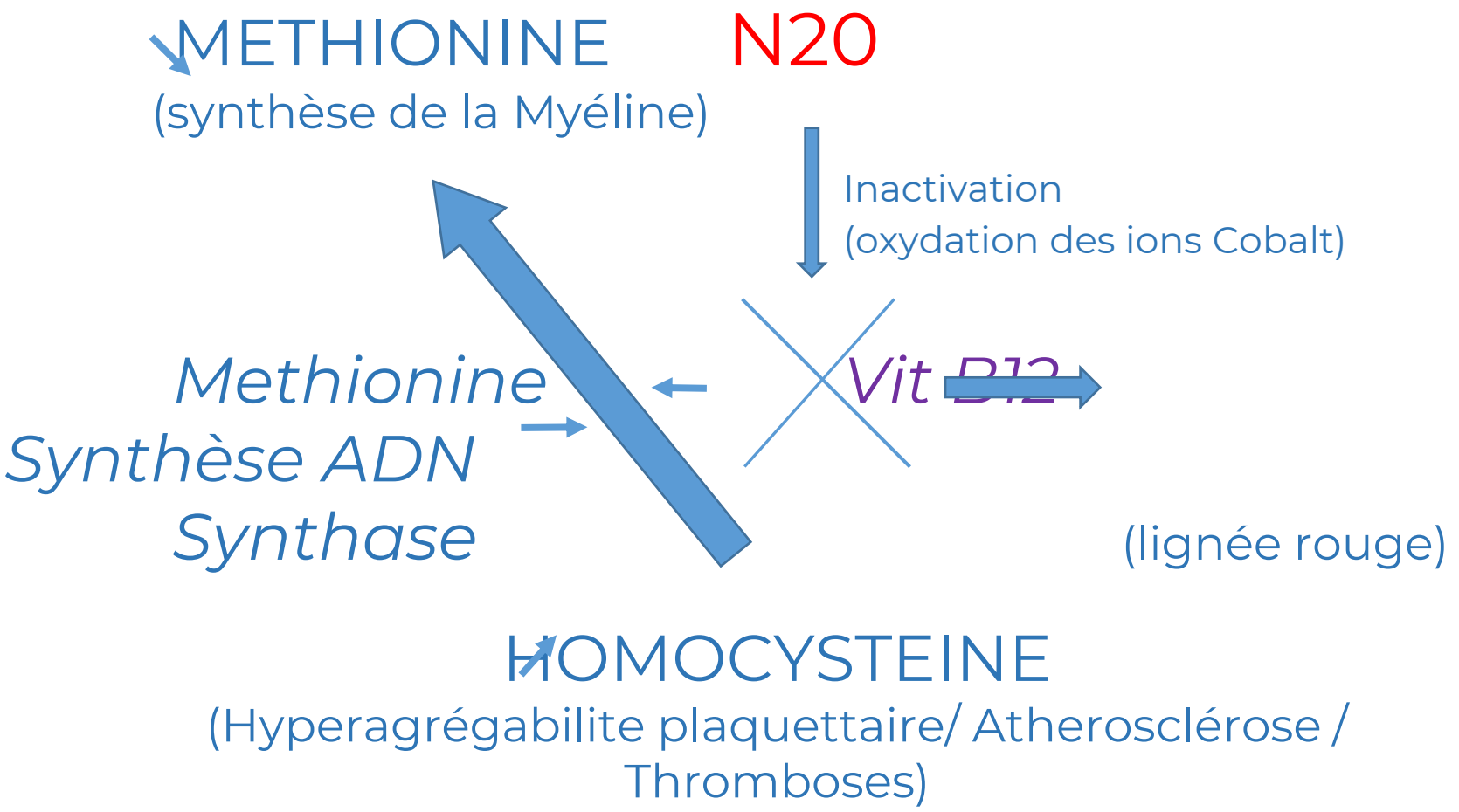
PHYSIOPATHOLOGIE

Inactivation vitamine B12



Dosage en Vitamine B12 (normale ou diminuée)
Dosage en homocysteine (augmentée)
Dosage en acide méthylmalonique (augmentée)

Pas de détection toxicologique du N20 en routine

Thrombosis Research 241 (2024) 109096

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Letter to the Editors-in-Chief

Thromboembolic complications following recreational use of nitrous oxide: A French Addictovigilance alert

ARTICLE INFO

Keywords
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Thrombosis
Risk factors
Hyperhomocysteinemia

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Table 1
Characteristics of thromboembolic cases subjects.

	Addictovigilance (AV) N = 33	Literature (LC) N = 28	ALL N = 61
PATIENTS			
- Sex (man)	27/33	20/28	47/61 (77 %)
- Age (mean, min, max)	23.9 (16; 38)	25.1 (16; 38)	24.4 (16; 38)
REPORTED N_2O CONSUMPTION			
- Frequency (N filled)	20/33	15/28	35/61
◦ Daily	11/20	10/15	21/35 (60 %)
◦ Weekly, multiweekly	4/20	3/15	7/35 (20 %)
◦ Monthly or multi monthly	2/20	1/15	3/35 (8.6 %)
◦ Occasional consumption	3/20	1/15	4/35 (11.4 %)
- Quantity (N filled)[a]	16/33 Mostly cylinders, up to 18/day	16/28 Heterogeneous units	32/61 Very high
- Length of time (N filled)	12/33	12/28	24/61
◦ <1 month	1/12	2/12	3/24 (12.5 %)
◦ 1–12 month(s)	7/12	7/12	14/24 (58.3 %)
◦ >12 months	4/12	3/12	7/24 (29.2 %)
ASSOCIATED USE REPORTED			
- Alcohol	12	1	13 (21.3 %)
- Tobacco	12	11	23 (37.7 %)
- Cannabis	12	2	14 (22.9 %)
- Other drugs	2 (cocaine, ecstasy)	2	4 (6.5 %)
REPORTED RISK FACTORS (other than tobacco)			
- Arterial risk factors	7	4	11[b] (18 %)
- Venous risk factors	12	5	17[c] (27.9 %)
BIOLOGY			
- Vit B12 deficiency (N/N filled)[d]	14/18	13/24	27/42 (64.3 %)
- Hyperhomocysteinemia (N/N filled)[e]	20/20	23/25	43/45 (95.6 %)
◦ Between 50 and 100 µmol/L	4/17	8/20	12/37
◦ Between 100 and 200	6/17	4/20	10/37

[c] Mainly history (5) or family history (3) of thromboembolic events and immobilisation (4).
[d] Vit B12 deficiency is defined by < 147 pmol/L or 200 pg/mL.
[e] Hyperhomocysteinemia is defined by > 15 µmol/L.
[f] Folates deficiency is defined according to each laboratory's standards (specified in case reports).

Table 2
Reported effects and associated risk factors.

Reported effect	Addictovigilance (AV) N = 33	Literature (LC) N = 28	ALL N = 61
VENOUS THROMBOEMBOLIC EVENTS[a]	28/33 (84.8 %)	20/28 (71.4 %)	48/61 (78.7 %)
- Pulmonary embolism	12/28	11/20	23/48 (47.9 %)
- Deep venous thrombosis	17/28	6/20	23/48 (47.9 %)
- Cerebral venous thrombosis	4/28	8/20	12/48 (25 %)
- Others	1/28	0/20	1/48 (2.1 %)
No venous risk factors reported	16/28 (57.1 %)	16/20 (80 %)	32/48 (66.7 %)
- Among these subjects			
◦ Hyperhomocysteinemia (N/N filled)	8/8	14/14	22/22 (100 %)
◦ Associated neurological effects	9/16	7/16	16/32 (50 %)
ARTERIAL THROMBOEMBOLIC EVENTS[a]	5/33 (15.2 %)	8/28 (28.6 %)	13/61 (21.3 %)
- Stroke	4/5	2/8	6/13 (46.2 %)
- Acute coronary syndrome/ myocardial infarction	1/5	4/8	5/13 (38.5 %)
- Other arterial thrombosis	0/5	3/8	3/13 (23.1 %)
No smoker, no other arterial risk factors reported	4/5 (80 %)	3/8 (37.5 %)	7/13 (53.8 %)
- Among these subjects			
◦ Hyperhomocysteinemia (N/N filled)	3/3	3/3	6/6 (100 %)
◦ Associated neurological effects	1/4	0/3	1/7 (14.3 %)
EVOLUTION (N/N filled)			
- Recovered	7/31	6/15	13/46 (28.3 %)
- In recovery at time of notification/publication	21/31	2/15	23/46 (50 %)
- Not recovered/sequelae	2/31	7/15	9/46 (19.6 %)
- Death	1/31	0/15	1/46 (2.2 %)

[a] A patient may have several effects.

ALERTE

Communiqué de l'association française des centres d'addictovigilance et de la société française de médecine vasculaire

addictovigilance.fr

SFMV

COMPLICATIONS THROMBOEMBOLIQUES ASSOCIÉES AU PROTOXYDE D'AZOTE NON MÉDICAL

L'association française des centres d'addictovigilance alerte sur l'augmentation du nombre de cas d'évènements thromboemboliques en lien avec une consommation de protoxyde d'azote. [1-3] Il est utilisé essentiellement sous forme de grands contenants appelés bonbonnes à l'aide de ballons de baudruche ; majoritairement dans les populations jeunes et étudiantes ; peu de consommations associées ; initialement dans des contextes festifs ; à des fins euphorisantes, ou d'apaisement de la douleur morale. [3]

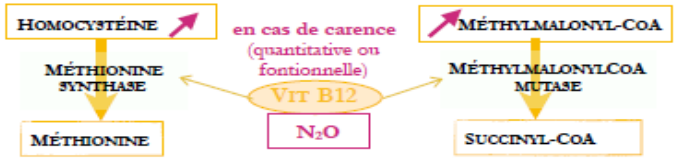
1. UN CONSTAT ALARMANT

Les cas d'évènements thromboemboliques en lien avec une consommation de protoxyde d'azote déclarés au réseau français d'addictovigilance (n=33) et ceux publiés dans la littérature scientifique (n=28) ont été analysés conjointement par les pharmacologues addictovigilants et par les médecins vasculaires du CHU de Nantes. [4]

Le protoxyde d'azote (N_2O) semble favoriser la survenue de complications thromboemboliques, principalement veineuses (80 % des cas, notamment EP, TVP, thrombophlébite cérébrale) mais aussi artériels (AVC, SCA,…). Les personnes concernées sont des sujets jeunes, dont plus de la moitié n'a pas de facteur de risque associé, mais qui présentent néanmoins presque systématiquement un déficit fonctionnel en vitamine B12 responsable d'une hyperhomocystéinémie. Des effets indésirables neurologiques sont associés dans près d'un cas sur deux (notamment des neuropathies périphériques et des scléroses combinées de la moelle). [4]

2. POURQUOI ? UN DÉFICIT FONCTIONNEL EN VITAMINE B12

Le protoxyde d'azote est responsable d'une oxydation irréversible de l'ion cobalt de la vitamine B12 (cyanocobalamine), cofacteur essentiel de plusieurs enzymes impliquées dans la synthèse de l'ADN, l'hématopoïèse ou encore la myélinisation du système nerveux central. [5]



Ainsi, cette modification de la vitamine B12 par le N_2O la rend non fonctionnelle, et entraine une accumulation de méthylmalonyl-CoA et d'homocystéine. Ce déficit étant **fonctionnel**, le dosage quantitatif de la vitamine B12 peut paraître normal ou peu altéré. Le N_2O n'étant pas identifiable en routine dans le sang, lorsqu'une consommation de N_2O est suspectée ou avérée, **l'homocystéine peut être dosée.** [4] L'hyperhomocystéinémie est responsable d'un état prothrombotique (par un mécanisme complexe incluant dysfonction endothéliale, altération du collagène et de l'élastine) et constitue **un facteur de risque indépendant connu de complications vasculaires** thromboemboliques, veineuses ou artérielles. [6]

3. QUE FAIRE ?

Pour prévenir et gérer ces effets, la première étape est l'identification de l'intoxication : **face à un patient jeune (<40 ans), présentant un évènement thromboembolique veineux ou artériel, les professionnels de santé doivent systématiquement se renseigner sur la consommation de protoxyde d'azote.** Un dosage plasmatique de la vitamine B12 et de l'homocystéine (à jeun pour l'homocystéine) peuvent être utiles et apporter des arguments en faveur de cette étiologie.

La prévention des **récidives** d'évènements vasculaires liés à la consommation de N_2O repose sur **l'arrêt total de sa consommation**. La supplémentation des patients en B12 est nécessaire mais ne suffit pas en cas de poursuite de la consommation de N_2O pour prévenir ou améliorer les effets (neurologiques, psychiatriques, thromboemboliques, etc). La prise en charge doit donc être **multidisciplinaire** : vasculaire et addictologique ; ces tableaux sont d'ailleurs régulièrement associés à d'autres complications (neurologiques, psychiatriques…) qu'il convient de rechercher.

Si vous diagnostiquez des cas, il convient d'en informer votre CEIP-A (Centre d'Evaluation et d'Information sur la Pharmacodépendance-Addictovigilance) de rattachement (contacts : https://addictovigilance.fr/centres/).

PHARMACOLOGIE CLINIQUE Marseille

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Complications vésicales et néphrologiques graves par **l'usage répété et réaulier de kétamine**

Cystite interstitielle : dysurie, mictions fréquentes, urgenturies, douleur supra-pubienne, hématurie,...

Diminution de la capacité vésicale avec lésions érythémateuses similaire au carcinome *in situ*

Sténose bilatérale des uretères

Rétention urinaire chronique

Hydronéphrose, Insuffisance rénale

Nécrose papillaire

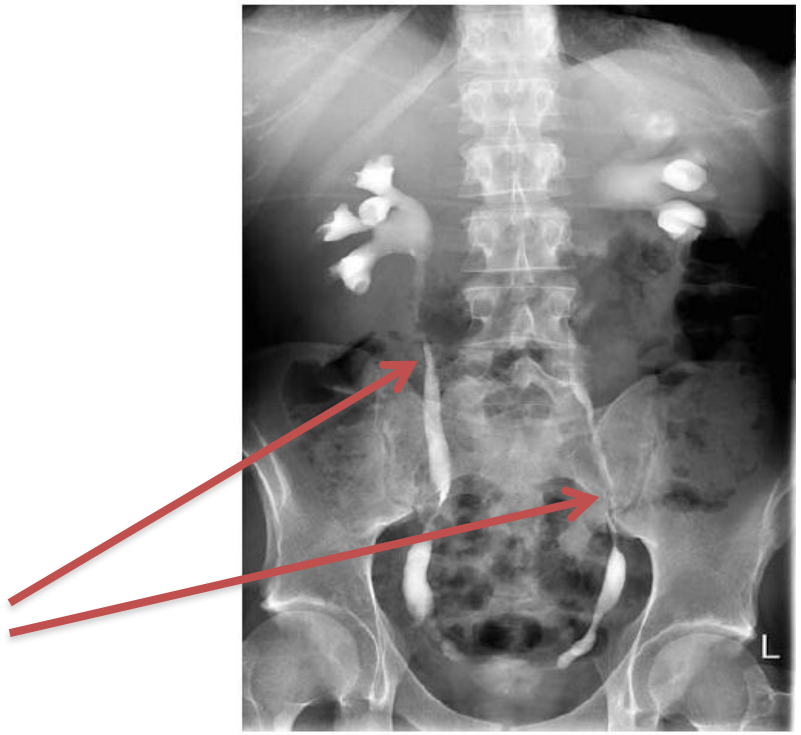

Figure 1 Intravenous urogram showing bilateral ureteric stricturing and a contracted bladder.

Gully et al, Nephrologie 2017
Jhang et al, Neurourology & urodynamics 2017
Rasion et al, BMJ, 2015
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Wood et al, B J urology 2011,
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Huang et al, Kidney international, 2011

Quelle plausibilité biologique ?

METABOLIC, ENDOCRINE, AND GENITOURINARY PATHOBIOLOGY

Ketamine-Induced Apoptosis in Normal Human Urothelial Cells

A Direct, N-Methyl-D-Aspartate Receptor–Independent Pathway Characterized by Mitochondrial Stress

Simon C. Baker,* Saqib Shabir,* Nikolaos T. Georgopoulos,† and Jennifer Southgate*

From the Jack Birch Unit of Molecular Carcinogenesis, Department of Biology, University of York, York; and the Department of Biological Sciences,† School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom*

EFFET PHARMACOLOGIQUE DIRECT
Inflammation
Aptotose
Altération endothéliale

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journal homepage: www.elsevier.com/locate/toxlet

Mice are prone to kidney pathology after prolonged ketamine addiction

L.Y. Yeung, J.A. Rudd, W.P. Lam, Y.T. Mak, D.T. Yew*

School of Biomedical Sciences, Faculty of Medicine, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China

OPEN ACCESS Freely available online

PLOS ONE

'Special K' and a Loss of Cell-To-Cell Adhesion in Proximal Tubule-Derived Epithelial Cells: Modulation of the Adherens Junction Complex by Ketamine

Claire E. Hills[1]*, Tianrong Jin[2], Eleftherios Siamantouras[2], Issac K-K Liu[2], Kieran P. Jefferson[3], Paul E. Squires[1]

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Institut de Neurosciences des Systèmes

La méthoxetamine : aussi… analogue NMDA

Article

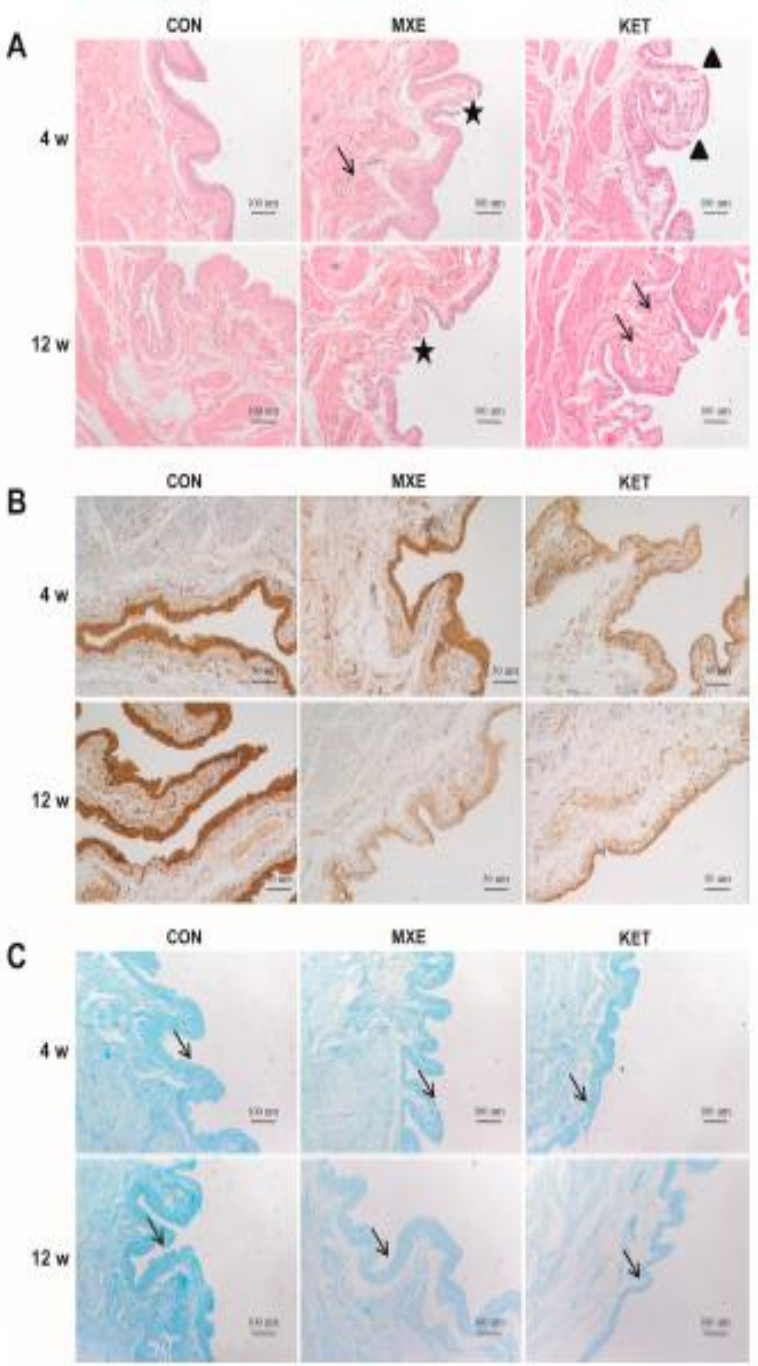
Ketamine Analog Methoxetamine Induced Inflammation and Dysfunction of Bladder in Rats

Qiang Wang [1,†], Qinghui Wu [1,†], Junpeng Wang [1], Yang Chen [1], Guihao Zhang [1], Jiawei Chen [1], Jie Zhao [2,*] and Peng Wu [1,*]

Micturition frequency of rats in different experimental groups

Duraion	CON	MXE	KET
4 weeks	0.33 ± 0.52	3.33 ± 1.03**	4.17 ± 1.17**
12 weeks	0.83 ± 0.75	4.50 ± 1.52**	6.50 ± 1.87**,#

Data are expressed as means ± SD. n=6 per group.



Mucosal injury in rat bladder tissue after MXE and KET a

Jusqu' à la chirurgie !

CYTOPLASTIE, CYSTECTOMIE

AVEC DERIVATION DES URETERES

Pain Physician 2017; 20:E431-E436 •

Retrospective Review

Clinical Outcome of Augmentation Enterocystoplasty for Patients with Ketamine-induced Cystitis

Yu Khun Lee, MD, Jia-Fong Jhang, MD, and Hann-Chorng Kuo, MD

treatment (new drug/intervention; established drug/procedure in new situation)

CASE REPORT

Autotransplantation for the management of ketamine ureteritis

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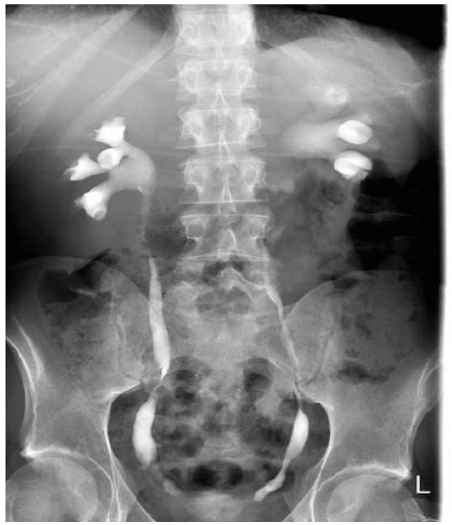
Accepted 9 March 2015

SUMMARY
Ketamine-associated cystitis is a well-recognised syndrome; yet upper urinary tract involvement remains poorly understood. We present the case of a 33-year-old man who developed ketamine-associated cystitis and ureteritis. The patient's severe bladder symptoms required subtotal cystectomy and orthotopic reconstruction. However, the associated ureteritis led to bilateral ureteric obstruction and renal failure. Bilateral autotransplantation with pyelovesicostomy was performed. This first case of autotransplantation for ketamine uropathy helps to demonstrate the potentially devastating effects of ketamine on the urinary tract.

BACKGROUND
Ketamine cystitis was first identified by Shahani *et al*[1]. It is characterised by irritative lower urinary tract symptoms and haematuria. Clinical findings include sterile pyuria and a low-capacity chronically inflamed bladder with ulceration. However, ketamine's effects on the upper tract remain largely unknown. We present this case of ketamine ureteritis to highlight its potentially devastating effects.



The French Journal of Urology 34 (2024) 102754

Contents lists available at ScienceDirect

The French Journal of Urology

journal homepage: www.elsevier.com/locate/fjurol

Recommendations

Management of ketamine cystitis: National guidelines from the French Association of Urology (CUROPF/CTMH)

Prise en charge des cystites à la kétamine : recommandations nationales de l'Association française d'urologie (CUROPF/CTMH)

Alice Bourillon [a,*], Jean Nicolas Cornu [b], François Herve [c], Raphael Pangui [d], Caroline Thuillier [e], Steeve Doizi [f], Souhil Lebdai [g], Benoit Peyronnet [a], And the members of the CUROPF 1the CTMH 2

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ARTICLE INFO

Keywords:
Ketamine cystitis
Ketamine induced uropathy
Ketamine

ABSTRACT

Objective: The objective of the CUROPF and CTMH was to establish recommendations about ketamine induced uropathy management.
Methods: A systematic review of the literature was conducted on Pubmed/Medline by the members of the French committees of female urology and male lower urinary tract symptoms focusing on the epidemiology, pathophysiology, diagnosis and treatment of ketamine induced uropathy, evaluating references and level of evidence.
Results: Recommendations include epidemiology, pathophysiology, diagnosis and treatment of ketamine induced uropathy. It represents a rising healthcare issue, with major augmentation of ketamine consumers and new patients across the world. Several pathophysiology pathways are suspected and need clinical validation. The diagnosis is clinical, with hyperactive bladder symptoms mostly including pollakiuria, but also lower urinary tract symptoms, and histological, requiring bladder biopsies to rule out carcinoma and show specific features and inflammation. Therapeutics are currently limited and non-specific, combining abstinence, hydrodistension, pentosane polysulfate and Botox injections. Complex reconstructive surgeries should be avoided and be considered as a last resort.
Conclusion: These guidelines should provide tools to help every physician confronted to ketamine induced uropathy patients, which represents a growing issue. Hopefully, this work will allow the improvement of the screening, management and care of ketamine induced uropathy in the future.

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journal homepage: www.elsevier.com/locate/fjurol

Letter to Editor

French Addictovigilance monitoring of ketamine and its analogues

Dear Editor,

We read with great interest the article entitled "Management of ketamine cystitis: national guidelines from the French Association of Urology (CUROPF/CTMH)" by A. Bourillon et al., published in the issue of *The French Journal of Urology* [1].

This is a particularly important and useful article in the context of the growing use of ketamine and its derivatives in France, either as a drug or as a medication. In 2024, ketamine has had its French marketing authorization extended to chronic pain and more specifically to refractory neuropathic pain.

In France, drug dependence assessment and information centers monitor and assess the clinical complications of psychoactive substances at risk of abuse in the framework of Addictovigilance, leading the French Drug Agency (ANSM) to take preventive and information measures [2]. Ketamine has been specifically monitored as a product with an abuse/dependence potential [3]. French Addictovigilance data have clearly shown that the repeated, regular and prolonged use of ketamine, whatever its purpose (recreational, therapeutic, addictive, chemsex, etc.) constitutes the breeding ground for the emergence of these urinary complications [3]. Their update in 2024 shows the extent of this regular use, often by nasal route, as shown by the increase of both serious addictovigilance reports and ketamine users among patients of addictology centers. Since 2020, esketamine (the S-enantiomer of ketamine) has been available in France as a nasal spray to treat severe forms of depression, associated to oral antidepressants. Under medical supervision, esketamine is self-administered twice a week during weeks 1–4 in the induction phase, followed by maintenance treatment once weekly during weeks 5–8, and then every 2 weeks or once weekly from week 9 forward. As mentioned in the Summary of product characteristics, in clinical studies with esketamine, despite no reported case of interstitial cystitis a higher rate of lower urinary tract symptoms was observed (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in esketamine-treated patients compared with placebo-treated patients. The expert panel the French Association for Biological Psychiatry and Neuropsychopharmacology recommends the use of esketamine as a first-line add-on agent, in accordance with the current regulatory framework in France, and the use of intravenous ketamine as a second-line add-on agent, off-label in treatment resistant depression in France.

Besides, regarding the synthetic analogues of ketamine, which are substances that mimic its effects with much greater pharmacological potency, lead to more intense or longer-lasting effects. Among these synthetic products, methoxetamine administered to animals also induces urinary abnormalities objectified in experimental situations (versus placebo, versus ketamine).

In conclusion, all these data support a class effect with ketamine and its analogues at the origin of the urinary complications comprehensively described by Bourillon et al. They underline the essentiality of the close collaboration between urologists and pharmacologists from Addictovigilance centres in order to be more reactive to the emergence of these products, their methods of use and their complications. Furthermore, these data emphasize the importance of extending the patient interview to all psychoactive substances beyond alcohol and tobacco.

Disclosure of interest

The authors declare that they have no competing interest.

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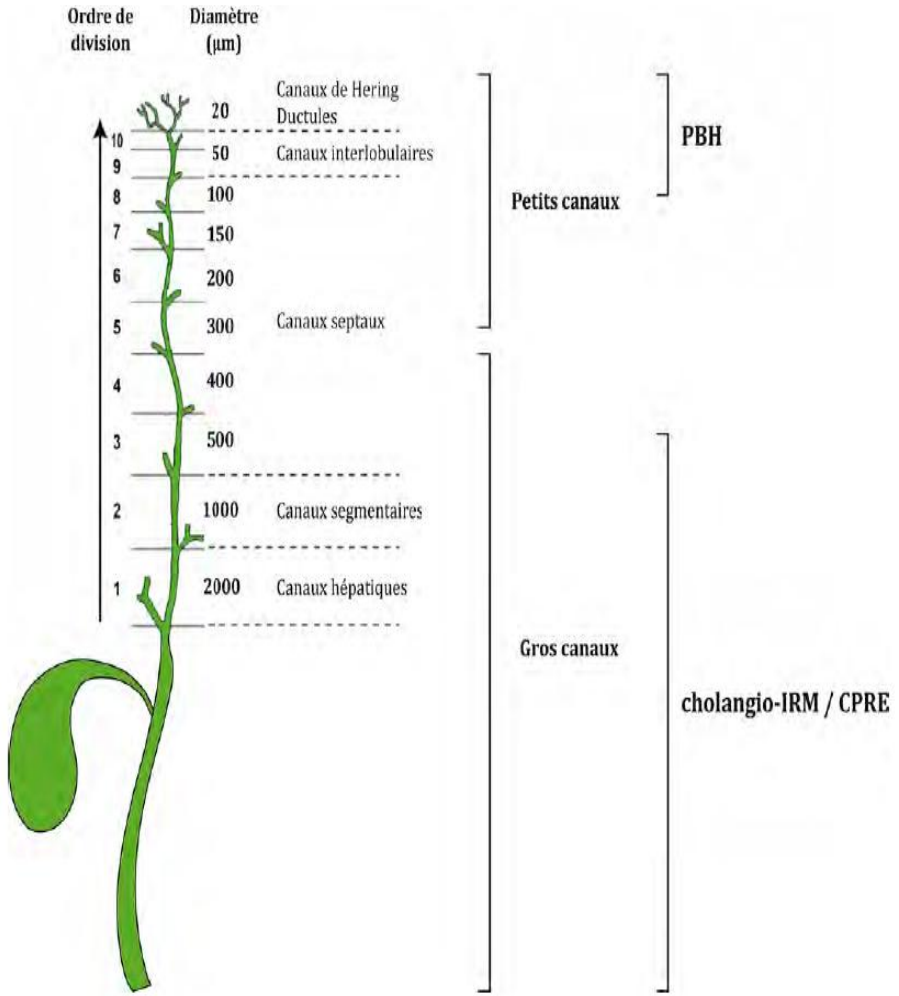
Les cholangiopathies inflammatoires (ou cholangites)

- Maladies caractérisées par une inflammation primitives ou secondaires des voies biliaires

- Se manifestant le plus souvent par des signes de cholestase (PAL >1,5 et GGT > 3N)



PHARMACOLOGIE CLINIQUE Marseille

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Pour citer cet article : Corpechot C. Cholangiopathies inflammatoires – Bases sémiologiques et nosologiques. *Hépato Gastro* 2014 ; 21 : 662-678. doi : 10.1684/hpg.2014.1061

Étiologies

Mécanisme princeps	Maladies
Immunologique	CBP, CSP, sarcoïdose, cholangite à IgG4, rejet de greffe, GVH, mastocytose, histiocytose, ...
Toxique	Médicaments, formaldéhyde, éthanol, 5FUDR, kétamine
Infectieux	Stase biliaire, infections opportunistes (CMV, cryptosporidie), échinococcose, HCV, HEV
Ischémique	Thrombose ou embolisation artérielle, lésion vasculaire chirurgicale, réanimation
Génétique	Mucoviscidose, LPAC, maladie de Caroli, FHC, Kyste du cholédoque, atrésie

Cirrhose biliaire primitive

Cholangite sclérosante primitive

mixte, toxique et ischémique. La consommation chronique de kétamine, produit d'anesthésie générale parfois détourné à des fins de toxicomanie, peut être à l'origine d'une cholangite inflammatoire d'évolution sténosante [20].

PHARMACOLOGIE CLINIQUE Marseille

Hôpitaux Universitaires de Marseille | ap·hm

Pour citer cet article : Corpechot C. Cholangiopathies inflammatoires – Bases sémiologiques et nosologiques. *Hépato Gastro* 2014 ; 21 : 662-678. doi : 10.1684/hpg.2014.1061

Les premiers cas publiés en 2009

Hong Kong Med J 2009;15:53-6

MEDICAL PRACTICE

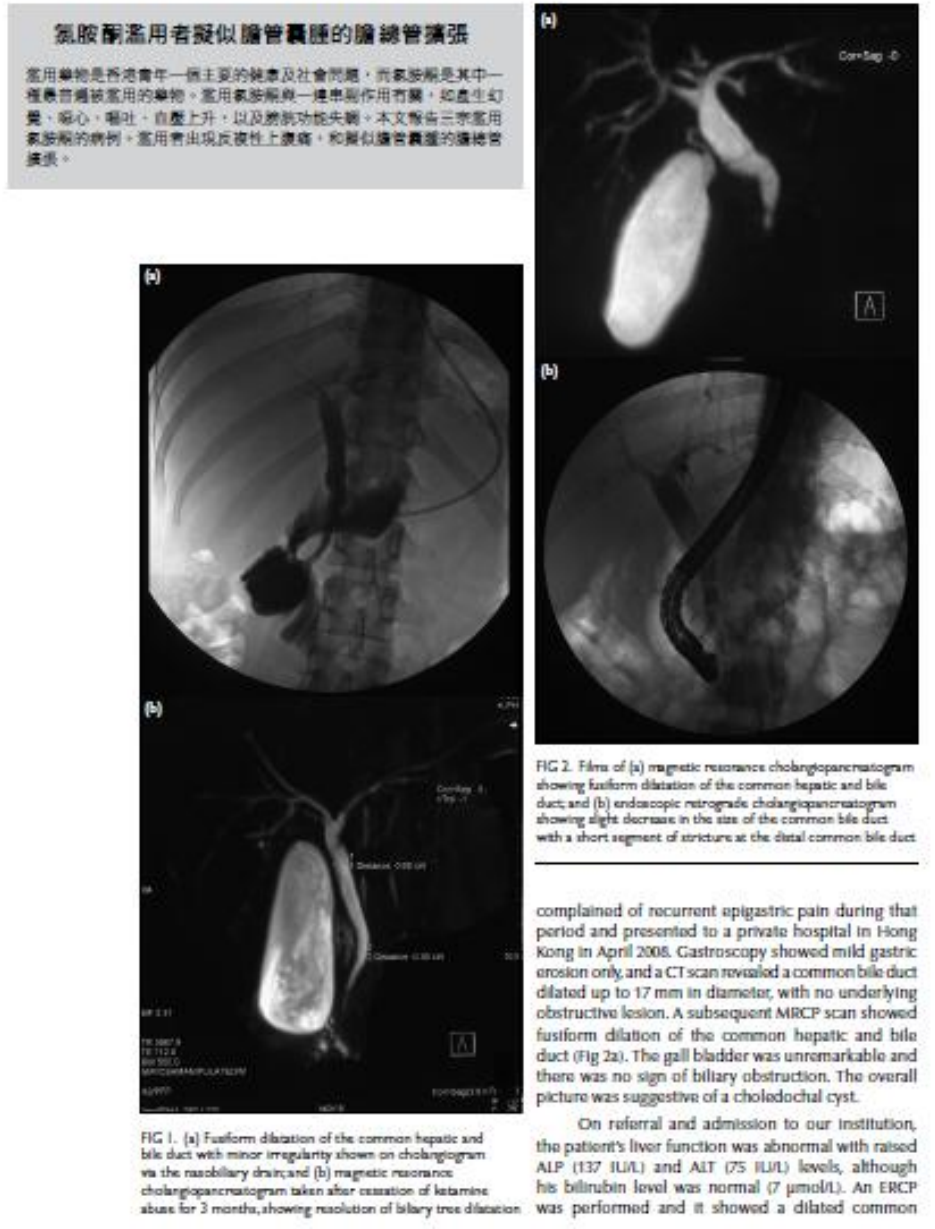
Dilated common bile ducts mimicking choledochal cysts in ketamine abusers

EXPEDITED PAPER

SW Wong 王韶宏
KF Lee 李傑輝
John Wong 黃 創
Wilson WC Ng 吳咏志
YS Cheung 張宇新
Paul BS Lai 賴寶山

Substance abuse is a major health and social problem among Hong Kong youth and ketamine is the drug most commonly abused. Ketamine abuse is associated with a series of side-effects that include hallucination, nausea, vomiting, elevation of blood pressure, and urinary bladder dysfunction. Here we report three cases of ketamine abuse in which the abusers presented with recurrent epigastric pain and dilated common bile ducts that mimicked choledochal cysts on imaging. The dilated biliary tree may occur more frequently than was once assumed.

Femme de 21 ans – douleurs épigastriques récurrentes
Ketamine en usage régulier depuis 18 mois
PAL élevée. Dilatation de la VBP
Arrêt de la kétamine. Amélioration
Reprise de la kétamine- Récidive clinique, biologique et radiologique



氯胺酮濫用者疑似膽管囊腫的膽總管擴張

濫用藥物是香港青年一個主要的健康及社會問題，而氯胺酮是其中一種最常被濫用的藥物。濫用氯胺酮與一連串副作用有關，如產生幻覺、噁心、嘔吐、血壓上升，以及膀胱功能失調。本文報告三宗濫用氯胺酮的病例，濫用者出現反復性上腹痛，和類似膽管囊腫的膽總管擴張。

FIG 1. (a) Fusiform dilatation of the common hepatic and bile duct with minor irregularity shown on cholangiogram via the nasobiliary drain; and (b) magnetic resonance cholangiopancreatogram taken after cessation of ketamine abuse for 3 months, showing resolution of biliary tree dilatation

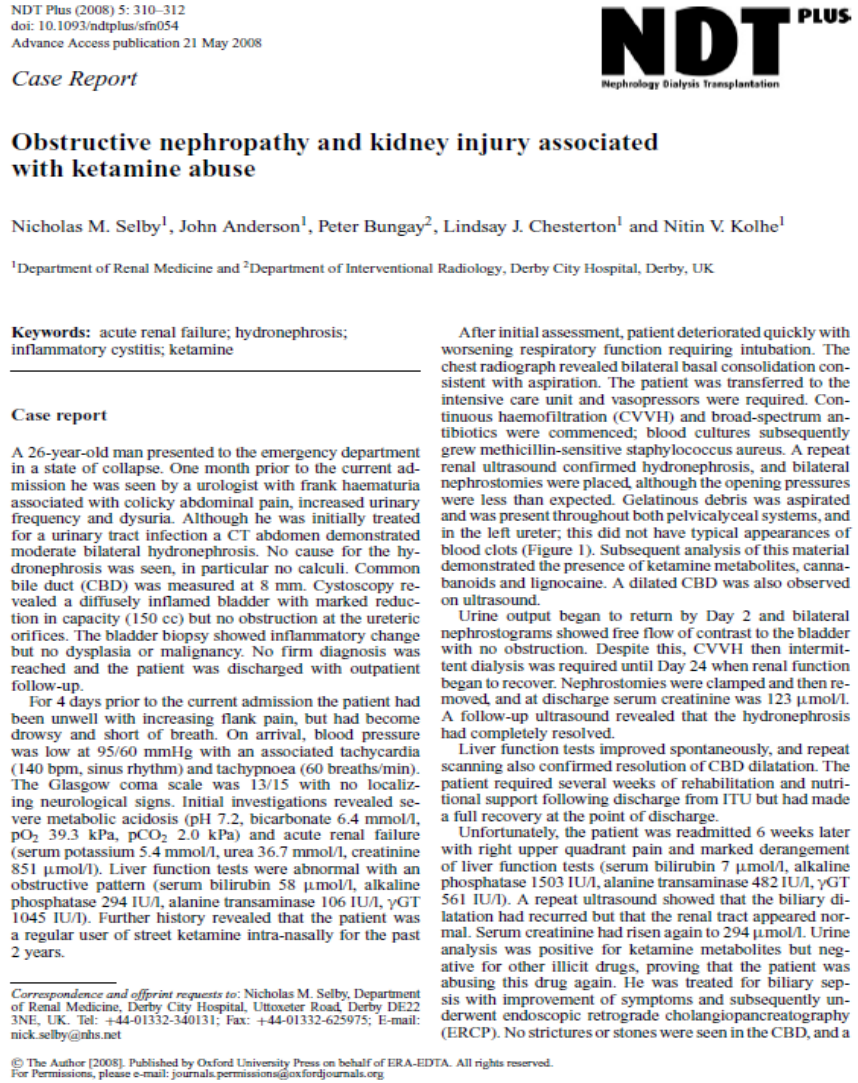
FIG 2. Films of (a) magnetic resonance cholangiopancreatogram showing fusiform dilatation of the common hepatic and bile duct; and (b) endoscopic retrograde cholangiopancreatogram showing slight decrease in the size of the common bile duct with a short segment of stricture at the distal common bile duct

complained of recurrent epigastric pain during that period and presented to a private hospital in Hong Kong in April 2008. Gastroscopy showed mild gastric erosion only, and a CT scan revealed a common bile duct dilated up to 17 mm in diameter, with no underlying obstructive lesion. A subsequent MRCP scan showed fusiform dilation of the common hepatic and bile duct (Fig 2a). The gall bladder was unremarkable and there was no sign of biliary obstruction. The overall picture was suggestive of a choledochal cyst.

On referral and admission to our institution, the patient's liver function was abnormal with raised ALP (137 IU/L) and ALT (75 IU/L) levels, although his bilirubin level was normal (7 μmol/L). An ERCP was performed and it showed a dilated common

Et finalement sans doute déjà en 2008

- Cas d'un Homme de 26 ans
- Usager régulier de kétamine par voie nasale depuis 2 ans avec une atteinte urinaire marquée (capacité vésicale à 150 cc, hydronéphrose marquée)…
- *et une cholestase (PAL et GGT augmenté – associé à une dilatation de la voie biliaire principale)*



NDT Plus (2008) 5: 310–312
doi: 10.1093/ndtplus/sfn054
Advance Access publication 21 May 2008

NDT PLUS
Nephrology Dialysis Transplantation

Case Report

Obstructive nephropathy and kidney injury associated with ketamine abuse

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Keywords: acute renal failure; hydronephrosis; inflammatory cystitis; ketamine

Case report

A 26-year-old man presented to the emergency department in a state of collapse. One month prior to the current admission he was seen by a urologist with frank haematuria associated with colicky abdominal pain, increased urinary frequency and dysuria. Although he was initially treated for a urinary tract infection a CT abdomen demonstrated moderate bilateral hydronephrosis. No cause for the hydronephrosis was seen, in particular no calculi. Common bile duct (CBD) was measured at 8 mm. Cystoscopy revealed a diffusely inflamed bladder with marked reduction in capacity (150 cc) but no obstruction at the ureteric orifices. The bladder biopsy showed inflammatory change but no dysplasia or malignancy. No firm diagnosis was reached and the patient was discharged with outpatient follow-up.

For 4 days prior to the current admission the patient had been unwell with increasing flank pain, but had become drowsy and short of breath. On arrival, blood pressure was low at 95/60 mmHg with an associated tachycardia (140 bpm, sinus rhythm) and tachypnoea (60 breaths/min). The Glasgow coma scale was 13/15 with no localizing neurological signs. Initial investigations revealed severe metabolic acidosis (pH 7.2, bicarbonate 6.4 mmol/l, pO_2 39.3 kPa, pCO_2 2.0 kPa) and acute renal failure (serum potassium 5.4 mmol/l, urea 36.7 mmol/l, creatinine 851 μmol/l). Liver function tests were abnormal with an obstructive pattern (serum bilirubin 58 μmol/l, alkaline phosphatase 294 IU/l, alanine transaminase 106 IU/l, γGT 1045 IU/l). Further history revealed that the patient was a regular user of street ketamine intra-nasally for the past 2 years.

After initial assessment, patient deteriorated quickly with worsening respiratory function requiring intubation. The chest radiograph revealed bilateral basal consolidation consistent with aspiration. The patient was transferred to the intensive care unit and vasopressors were required. Continuous haemofiltration (CVVH) and broad-spectrum antibiotics were commenced; blood cultures subsequently grew methicillin-sensitive staphylococcus aureus. A repeat renal ultrasound confirmed hydronephrosis, and bilateral nephrostomies were placed, although the opening pressures were less than expected. Gelatinous debris was aspirated and was present throughout both pelvicalyceal systems, and in the left ureter; this did not have typical appearances of blood clots (Figure 1). Subsequent analysis of this material demonstrated the presence of ketamine metabolites, cannabanoids and lignocaine. A dilated CBD was also observed on ultrasound.

Urine output began to return by Day 2 and bilateral nephrostograms showed free flow of contrast to the bladder with no obstruction. Despite this, CVVH then intermittent dialysis was required until Day 24 when renal function began to recover. Nephrostomies were clamped and then removed, and at discharge serum creatinine was 123 μmol/l. A follow-up ultrasound revealed that the hydronephrosis had completely resolved.

Liver function tests improved spontaneously, and repeat scanning also confirmed resolution of CBD dilatation. The patient required several weeks of rehabilitation and nutritional support following discharge from ITU but had made a full recovery at the point of discharge.

Unfortunately, the patient was readmitted 6 weeks later with right upper quadrant pain and marked derangement of liver function tests (serum bilirubin 7 μmol/l, alkaline phosphatase 1503 IU/l, alanine transaminase 482 IU/l, γGT 561 IU/l). A repeat ultrasound showed that the biliary dilatation had recurred but that the renal tract appeared normal. Serum creatinine had risen again to 294 μmol/l. Urine analysis was positive for ketamine metabolites but negative for other illicit drugs, proving that the patient was abusing this drug again. He was treated for biliary sepsis with improvement of symptoms and subsequently underwent endoscopic retrograde cholangiopancreatography (ERCP). No strictures or stones were seen in the CBD, and a

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PHARMACOLOGIE CLINIQUE Marseille

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amU Aix Marseille Université

Institut Neuro Systèmes

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ORIGINAL ARTICLE

Patterns of ketamine use among people with substance use disorder in France: Multisource analysis of the data from the French Addictovigilance Network

Pauline Gandolfo[1,2] | Thomas Soeiro[1,2] | Élisabeth Jouve[1,2] | Bruno Revol[3] | Amélie Daveluy[4] | Célian Bertin[5] | Céline Eiden[6] | Valérie Gibaja[7] | Leila Chaouachi[8] | Marie-Christine Pérault-Pochat[9] | Cécile Chevallier[10] | Aurélie Aquizérate[11] | Reynald Le Boisselier[12] | Louise Carton[13] | Maryse Lapeyre-Mestre[14] | Élisabeth Frauger[1,2] | Clémence Lacroix[1,2] | Joëlle Micallef[1,2]

FIGURE 1 Number and prevalence of ketamine users with substance use disorder in the OPPIDUM program from 2012 to 2021.

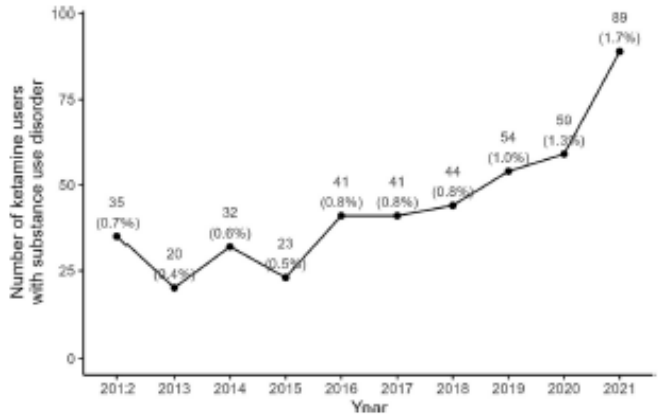

TABLE 4 Notable cases of hepatic complication in ketamine users with substance use disorder in the BNPV from July 2020 to December 2022.

Age	Sex	Ketamine use	Clinical complication and care
15 years old	Man	Ketamine at a rave party, with LSD, methadone, and MDMA	Helicopter transport to emergency Main clinical complications included hepatic cytolysis, renal insufficiency with rhabdomyolysis, and deep sedation improved with naloxone
22 years old	Man	10 g/day for 6 months, via nasal route	Mild disruption of liver function with a cytolytic pattern that worsened within 1 week Sterile cystitis with functional voiding symptom; previous urological assessment 4 months prior was normal
23 years old	Man	1 to 5 g/day over several years, via nasal route	Anicteric cholestasis and ALAT-predominant cytolysis; second hospitalization for the same reason; diagnosis of cholestasis secondary to several years of high-dose ketamine use; mention of damage of the sphincter of Oddi Altered general condition Functional urinary symptoms with bilateral pyelonephritis and right ureterohydronephrosis; probable chronic cystitis in relation to intranasal ketamine use
Unknown	Man	Increase of ketamine use over the past month for pain relief	Epigastric abdominal pain for several months Cytolysis and cholestasis with dilation of the bile ducts on abdominal CT and MRI leading to a diagnosis of cholangitis
21 years old	Unknown	Ketamine and MDMA	Intubated due to neurological failure and admission in intensive care unit Positive urine toxicology tests for midazolam, amphetamines, and MDMA Multi-organ failure and fulminant hepatitis due to drug use Transfer to a neurology department for rehabilitation
19 years old	Man	Increase of ketamine use for pain relief, started 6 months ago, via nasal route	Digestive bleeding of biliary origin; anemia requiring blood transfusion Dilation of gall bladder leading to cholecystectomy Acute hepatitis

Cas Addictovigilance de 2020 à 2022

Cas d’addictovigilance

- H de 23 ans
- Kétamine par voie nasale consommation depuis 5 ans , dont les 3 dernières années de manière quotidienne : 1 à 5g/j
- ATCD : suivi en Urologie (Troubles fonctionnels urinaires sur pyélo-urétérite bilatérale et urétéro-hydronéphrose)
- Hospitalisé en service d'hépato-gastro-entérologie pour altération de l'état général et perturbation du bilan hépatique : cholestase anictérique
- A l'entrée : PAL 557U/L, GGT 1999U/L ALAT 162 U/L ASAT 66 U/L, TP 53%
- Amélioration du bilan hépatique après sevrage
- Suivi addictologique organisé

Description de cholangites dans des situations cliniques différentes dont le point commun est l'utilisation prolongée/répétée de doses élevées de kétamine

Douleur chronique

LIVER

CASE REPORT

Ketamine as a possible cause of cirrhosis in a patient with chronic pain

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ABSTRACT
Ketamine has been typically administered in short-term, few doses in the clinical setting of acute pain. Its hallucinogenic side effects have made it popular as a recreational drug. Reports of urological, biliary and liver abnormalities have been reported, mainly in cases of abuse. It is now increasingly used for chronic pain conditions, and here we report liver abnormalities and ultimately cirrhosis in an adult on regular ketamine for chronic facial pain. Abnormal liver function tests were detected incidentally, and with no other cause for liver disease found, liver biopsy was performed. This showed fibrosis with incomplete cirrhosis.

BACKGROUND
Ketamine, (*RS*)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone, is a non-competitive *N*-methyl-D-aspartate receptor antagonist, a drug with sedative, analgesic and anaesthetic properties. It has hallucinogenic and 'out of body' side-effects that have made it increasingly popular as a recreational drug.

Ketamine has typically been administered short-term as a few repeated doses in a clinical setting; therefore, most reports of the long-term effects have primarily been reported and investigated in chronic ketamine abusers. However, it is increasingly being used in the treatment of chronic pain problems refractory to other treatments in intravenous and oral preparations.[1]

Urological abnormalities such as ulcerative cystitis and hydronephrosis,[2] abnormal liver function tests (LFTs), and biliary dilatation have been recognised as complications of its use.

Here we report a case of chronic ketamine use in a chronic pain syndrome refractory to other measures in which the patient developed abnormal LFTs, dilatation of the biliary tree and progression to cirrhosis.

CASE PRESENTATION
A 55-year-old woman was referred by her GP to the gastroenterology department after she was found to have abnormal LFTs during routine blood tests. She gave a long history of chronic facial pain dating back over 20 years, refractory to treatment. Attempts to control her pain had required trials of many different medications including pethidine and codeine. Ketamine was added 10 years ago achieving a degree of control that the patient was reluctant to lose. The dose of ketamine had been stable at 150 mg QDS for 8 years, in addition to pethidine and paracetamol, with no other changes to her medications over that time period. Her past medical history included asthma controlled with inhalers, montelukast and carbocysteine; gastro-oesophageal reflux disease treated with pantoprazole and as required domperidone and ondansetron; and gallstone disease for which she had an uncomplicated laparoscopic cholecystectomy 8 years previously. At the time of referral, her facial pain was controlled, and she had no abdominal symptoms to report. There was no history of blood transfusion, significant foreign travel, intravenous drug abuse or contact with hepatitis. There was a family history of alcoholic cirrhosis, but she had no personal history of excess alcohol intake or clinical features to suggest alcohol abuse. Her weight was 68 kg and height 1.61 m, giving a body mass index of 26.2 kg/m^2.

To cite: Bevan R, Burke D. *Frontline Gastroenterology* 2014;5:208–210.

Chez les grands brulés

Ketamine restriction correlates with reduced cholestatic liver injury and improved outcomes in critically ill patients with burn injury

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Background & Aims: Ketamine-associated cholestatic liver injury is reported in patients with severe burn injury, but its association with patient outcome is unclear. We investigated the relationship between ketamine exposure, cholestatic liver injury, and outcome of critically ill patients with burn injury.

Methods: In a retrospective study, patients with severe burn injury were analysed across two periods: unrestricted ketamine prescription (ketamine-liberal) and capped ketamine dosage (ketamine-restricted). The primary endpoint was cholestatic liver injury, and the secondary endpoint was 3-month mortality. Binary logistic regression models and the revised electronic causality assessment method were used to measure the strength of associations and causality assessment, respectively.

Results: Of 279 patients (median age 51 [IQR 31–67] years; 63.1% men; burned surface area 28.5%, IQR 20–45%), 155 (56%) were in the ketamine-liberal group, and 124 (44%) were in the ketamine-restricted group, with comparable clinical characteristics, except for ketamine exposure (median doses 265.0 [IQR 0–8,021] mg and 20 [IQR 0–105] mg, respectively; p <0.001). A dose- and time-dependent relationship was observed between ketamine exposure and cholestatic liver injury. Ketamine restriction was associated with a reduced risk of cholestatic liver injury (adjusted odds ratio 0.16, 95% CI 0.04–0.50; p = 0.003) and with a higher probability of 3-month survival (p = 0.035). The revised electronic causality assessment method indicated that ketamine was probably and possibly the cause of cholestatic liver injury for 14 and 10 patients, respectively. Cholangitis was not observed in the ketamine-restricted group. In propensity-matched patients, the risk of 3-month mortality was higher (adjusted odds ratio 9.92, 95% CI 2.76–39.05; p = 0.001) in patients with cholestatic liver injury and ketamine exposure ≥10,000 mg. Other sedative drugs were not associated with liver and patient outcome.

Conclusions: In this cohort, ketamine restriction was associated with less cholestatic liver injury and reduced 3-month mortality.

Impact and implications: In a cohort of 279 critically ill patients with burn injury, ketamine was associated with a risk of liver bile duct toxicity. The risk was found to be dependent on both the dosage and duration of ketamine use. A restriction policy of ketamine prescription was associated with a risk reduction of liver injury and 3-month mortality. These findings have implications for the analgesia and sedation of critically ill patients with ketamine, with higher doses raising safety concerns.

Chez les patients COVID19 pris en charge en réanimation

Letters to the Editor JOURNAL OF HEPATOLOGY

Intravenous ketamine and progressive cholangiopathy in COVID-19 patients

Introduction
Ketamine, a nonbarbiturate general anaesthetic drug, has been proposed, off-label, as a second-line agent for maintenance sedation of patients with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, including those with Coronavirus infectious disease 2019 (COVID-19).[1] Cholangiopathy is reported after chronic exposure to ketamine, including in drug users and in burned patients.[2,3] We observed 5 COVID-19 patients from 5 distinct tertiary centers (1 in Germany, and 4 in France) with cholangiopathy after exposure to intravenous ketamine, between March 20, 2020 and April 6, 2020, during the first pandemic wave in Europe. Liver injury was dose-dependent, progressive, and total ketamine exposure correlated with outcome, including liver-related death.

Patients
The median (range) age of these patients was 59 (35–65) years, and 3 (60%) were males. Underlying conditions included: uncomplicated hypertension (3 patients), uncomplicated diabetes mellitus (2 patients), kidney transplantation (1 patient with a 53 mL/min/1.73 m^2 glomerular filtration rate), HBV infection under pre-emptive antiviral treatment with entecavir (1 patient), resolved hepatitis B (1 patient), smoking (1 patient). All patients had normal liver function and none had cirrhosis. The median body mass index was 28 (21–33) kg/m^2. The initial median serum C-reactive protein (CRP) level was 160 (65–641) mg/L. All patients underwent mechanical ventilation for 40 (39–59) days. Nadir partial pressure of oxygen (PaO_2) and arterial oxygen saturation (SaO_2) were 50 (42–62) mmHg and 81 (71–93) percent, respectively. All patients received norepinephrine for 10 (2–15) days with a maximum dose of 0.4 (0.1–0.6) μg/kg/min. Maximum arterial lactate level was 2.4 (1.5–4.9) mmol/L. All patients developed acute kidney injury, and 3 (60%) required renal replacement therapy. Intravenous ketamine was given to all patients during 16 (6–26) days at a dose of 0.6 (0.1–2.2) mg/kg/h, totaling a cumulative dose of 9.5 (3.8–95.9) grams.

Initial serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and total bilirubin levels were 2.3 (1–22.5), 1.7 (0.4–6.0), 0.7 (0.3–6.8), 0.9 (0.3–1.2), and 0.6 (0.3–1.0) times the upper limit of normal (ULN) range, respectively, and peaked, under ketamine, at 9.0 (5.7–22.6), 8.0 (3–12), 30.7 (18.6–248), 9.2 (4.9–11.5), and 18.0 (1.6–27.5) times the ULN, respectively. All liver screens, including for hepatotropic viruses, were negative. The relationships between total ketamine exposure, initial CRP and maximum serum bilirubin levels in the in

Keywords: Ketamine; Cholestasis; Intrahepatic; Cholangiopathy; Cholangitis; COVID-19; Chemical and Drug Induced Liver Injury.
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Critical Care

RESEARCH Open Access

Long-term ketamine infusion-induced cholestatic liver injury in COVID-19-associated acute respiratory distress syndrome

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Abstract
Background: A higher-than-usual resistance to standard sedation regimens in COVID-19 patients suffering from acute respiratory distress syndrome (ARDS) has led to the frequent use of the second-line anaesthetic agent ketamine. Simultaneously, an increased incidence of cholangiopathies in mechanically ventilated patients receiving prolonged infusion of high-dose ketamine has been noted. Therefore, the objective of this study was to investigate a potential dose–response relationship between ketamine and bilirubin levels.

Methods: Post hoc analysis of a prospective observational cohort of patients suffering from COVID-19-associated ARDS between March 2020 and August 2021. A time-varying, multivariable adjusted, cumulative weighted exposure mixed-effects model was employed to analyse the exposure–effect relationship between ketamine infusion and total bilirubin levels.

Results: Two-hundred forty-three critically ill patients were included into the analysis. Ketamine was infused to 170 (70%) patients at a rate of 1.4 [0.9–2.0] mg/kg/h for 9 [4–18] days. The mixed-effects model revealed a positively correlated infusion duration–effect as well as dose–effect relationship between ketamine infusion and rising bilirubin levels (p < 0.0001). In comparison, long-term infusion of propofol and sufentanil, even at high doses, was not associated with increasing bilirubin levels (p = 0.421, p = 0.258). Patients having received ketamine infusion had a multivariable adjusted competing risk hazard of developing a cholestatic liver injury during their ICU stay of 3.2 [95% confidence interval, 1.3–7.8] (p = 0.01).

Conclusions: A causally plausible, dose–effect relationship between long-term infusion of ketamine and rising total bilirubin levels, as well as an augmented, ketamine-associated, hazard of cholestatic liver injury in critically ill COVID-19 patients could be shown. High-dose ketamine should be refrained from whenever possible for the long-term anal-gosedation of mechanically ventilated COVID-19 patients.

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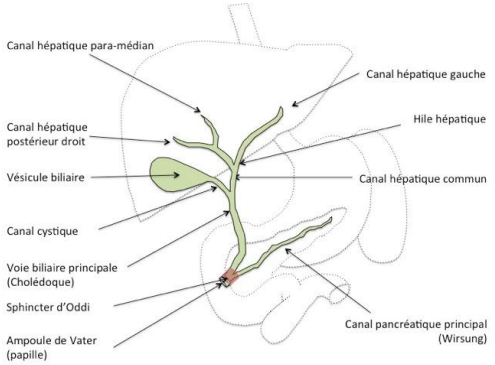
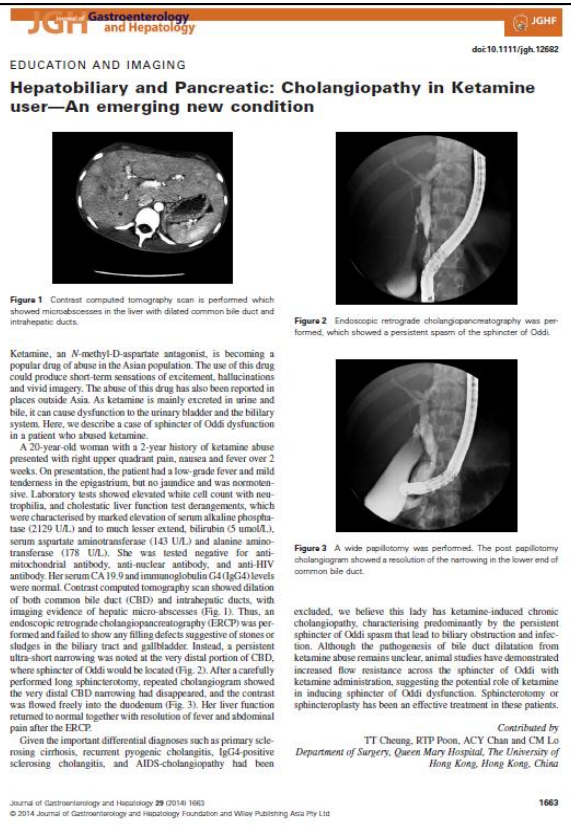
Hypothèses mécanistiques : dysfonctionnement du sphincter d'ODDI ?





JGH Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.12682

EDUCATION AND IMAGING

Hepatobiliary and Pancreatic: Cholangiopathy in Ketamine user—An emerging new condition

Figure 1 Contrast computed tomography scan is performed which showed microabscesses in the liver with dilated common bile duct and intrahepatic ducts.

Figure 2 Endoscopic retrograde cholangiopancreatography was performed, which showed a persistent spasm of the sphincter of Oddi.

Figure 3 A wide papillotomy was performed. The post papillotomy cholangiogram showed a resolution of the narrowing in the lower end of common bile duct.

Ketamine, an *N*-methyl-D-aspartate antagonist, is becoming a popular drug of abuse in the Asian population. The use of this drug could produce short-term sensations of excitement, hallucinations and vivid imagery. The abuse of this drug has also been reported in places outside Asia. As ketamine is mainly excreted in urine and bile, it can cause dysfunction to the urinary bladder and the biliary system. Here, we describe a case of sphincter of Oddi dysfunction in a patient who abused ketamine.

A 20-year-old woman with a 2-year history of ketamine abuse presented with right upper quadrant pain, nausea and fever over 2 weeks. On presentation, the patient had a low-grade fever and mild tenderness in the epigastrium, but no jaundice and was normotensive. Laboratory tests showed elevated white cell count with neutrophilia, and cholestatic liver function test derangements, which were characterised by marked elevation of serum alkaline phosphatase (2129 U/L) and to much lesser extend, bilirubin (5 umol/L), serum aspartate aminotransferase (143 U/L) and alanine aminotransferase (178 U/L). She was tested negative for anti-mitochondrial antibody, anti-nuclear antibody, and anti-HIV antibody. Her serum CA 19.9 and immunoglobulin G4 (IgG4) levels were normal. Contrast computed tomography scan showed dilation of both common bile duct (CBD) and intrahepatic ducts, with imaging evidence of hepatic micro-abscesses (Fig. 1). Thus, an endoscopic retrograde cholangiopancreatography (ERCP) was performed and failed to show any filling defects suggestive of stones or sludges in the biliary tract and gallbladder. Instead, a persistent ultra-short narrowing was noted at the very distal portion of CBD, where sphincter of Oddi would be located (Fig. 2). After a carefully performed long sphincterotomy, repeated cholangiogram showed the very distal CBD narrowing had disappeared, and the contrast was flowed freely into the duodenum (Fig. 3). Her liver function returned to normal together with resolution of fever and abdominal pain after the ERCP.

Given the important differential diagnoses such as primary sclerosing cirrhosis, recurrent pyogenic cholangitis, IgG4-positive sclerosing cholangitis, and AIDS-cholangiopathy had been excluded, we believe this lady has ketamine-induced chronic cholangiopathy, characterising predominantly by the persistent sphincter of Oddi spasm that lead to biliary obstruction and infection. Although the pathogenesis of bile duct dilatation from ketamine abuse remains unclear, animal studies have demonstrated increased flow resistance across the sphincter of Oddi with ketamine administration, suggesting the potential role of ketamine in inducing sphincter of Oddi dysfunction. Sphincterotomy or sphincteroplasty has been an effective treatment in these patients.

Contributed by
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CASE REPORT

Clinical Case Reports WILEY

Sphincter of oddi dysfunction induced by ketamine: A case report

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Key Clinical Message
Chronic ketamine use can lead to sphincter of oddi dysfunction (SOD), causing various hepatobiliary complications. Recognizing substance abuse history is vital for early detection. Timely intervention can prevent irreversible liver and pancreas damage.

Abstract
Ketamine is commonly abused as a recreational drug worldwide due to its ability to induce euphoria-like effects. Ketamine abuse is associated with many hepatobiliary side effects ranging from cholestasis to biliary sepsis and death. Here we present a case of a young 29-year female with upper abdominal pain due to SOD resulting from chronic use of ketamine. SOD can result in obstruction or dysfunction of the bile and pancreatic ducts. Ketamine induces SOD by activation of the muscarinic receptors in the sphincter of oddi. Detail history of substance abuse is crucial for early identification of ketamine-induced SOD. Early identification and treatment of this rare condition can prevent permanent injury to the liver and pancreas.

KEYWORDS
biliary diseases, drug abuse, low-dose ketamine, sphincter of oddi dysfunction

1 | INTRODUCTION

Ketamine is used as a recreational drug (street ketamine) due to its ability to induce euphoria and a trance-like state. Street ketamine can be inhaled, swallowed, or injected. It is abused in many parts of the world.[1] Although the recreational dosage is 15%–20% lower than the amount used for anesthesia, the extended and widespread recreational use of this substance has led to an increase in both side effects and fatalities.[2] In the United States, more than 2.3 million teens and adults used ketamine in their lifetime.[2]

Although the effects of ketamine on the urinary bladder have been widely reported, its effects on the bile duct and its management have not been extensively studied.[3] We report a rare case of the sphincter of oddi dysfunction (SOD) in a young female who presented to the hospital with abdominal pain.

- *Il s'agit d'une femme de 29 ans, consommatrice de kétamine depuis 8 ans (contexte récréationnel) qui se présente aux urgences pour une douleur abdominale du quadrant supérieur droit associé à des nausées et des vomissements.*
- *Les PAL sont à 116 UI/L.*
- *L'échographie abdominale met en évidence un canal biliaire commun (CBC) proéminent sans pathologie de la vésicule biliaire.*
- *Le TDM abdominal montre une dilatation du CBC mesurant jusqu'à 9 mm sans pathologie obstructive visible.*
- *La patiente est alors hospitalisée. Devant l'augmentation des PAL à 520 UI/L et l'augmentation des transaminases (ASAT à 489 UI/L et ALAT à 520 UI/L, il est décidé collégialement de réaliser une cholangiopancréatographie rétrograde par voie endoscopique (CPRE) qui montre la dilatation du CBC et catégorise le dysfonctionnement du sphincter d'Oddi en type 2.*
- *Une sphincterotomie est réalisée et une fluoroscopie post sphincterotomie confirme la réduction de la dilatation du CBC. L'évolution a été favorable avec la résolution de la symptomatologie.*

Diagnostic différentiel avec la cholangite sclérosante primitive ?

Histopathology

Histopathology 2025, **87**, 130–137. DOI: 10.1111/his.15435

Ketamine cholangiopathy: clinical features and liver biopsy findings

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Table 1. Clinical and serological features

Case	Age / gender	Duration (years)*	Liver-related symptoms	Urinary complication	AST (U/l) (10–35)	ALP (U/l) (30–130)	GGT (U/l) (1–55)	Bilirubin (μmol/l) (3–20)
1	60F	16	None	None	88	373	705	4
2	48 M	13	Abdominal pain	Cystitis, renal failure	21	377	79	11
3	25 M	3	Presented with jaundice and cholangitis	Cystitis	192	2709	2634	292
4	30 M	6	One episode of jaundice and cholangitis	Cystitis	80	1529	2486	24
5	30 M	10	None	Cystitis	118	1300	NA	9
6	34 M	6	None	Cystitis, renal failure	152	1650	NA	45
7	37 M	18	None	None	49	206	472	13
8	37F	24	Abdominal pain	Suspected cystitis	84	522	775	6

ALP, alkaline phosphatase; AST, aspartate aminotransferase; CK7, cytokeratin 7; GGT, gamma-glutamyl transferase; NA, not available.
*Duration of ketamine use until the diagnosis of cholangiopathy; M, male; F, female.

Les cholangiopathies à la ketamine miment la cholangite sclérosante primitive (biochimique, radiologique, et histologique)

Elles semblent moins inflammatoire et moins progressive que la cholangite sclérosante primitive

L'association avec une cystite, l'absence de maladie inflammatoire intestinale et une dilatation légère des voies biliaires extrahépatiques sans irrégularité constituent des indices diagnostiques potentiels.

PHARMACOLOGIE CLINIQUE Marseille

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Institut de Neurosciences des Systèmes

Complications ORL

Cocaïne et lésions destructrices centro-faciales

European Archives of Oto-Rhino-Laryngology (2022) 279:3257–3267
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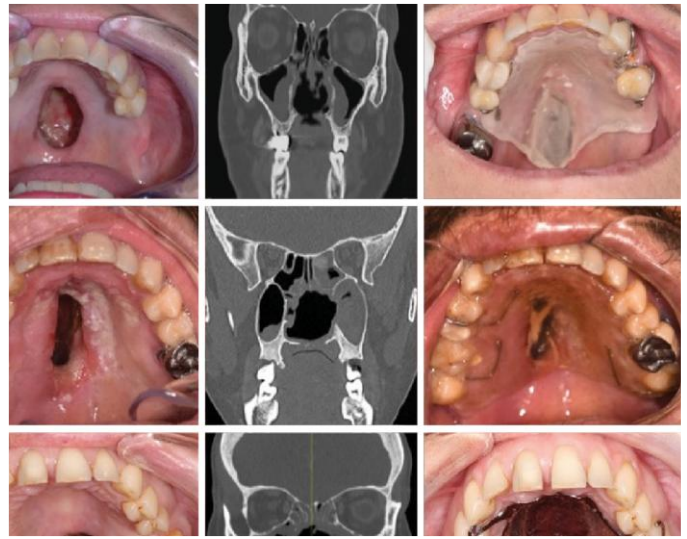
REVIEW ARTICLE

Distribution of cocaine-induced midline destructive lesions: systematic review and classification

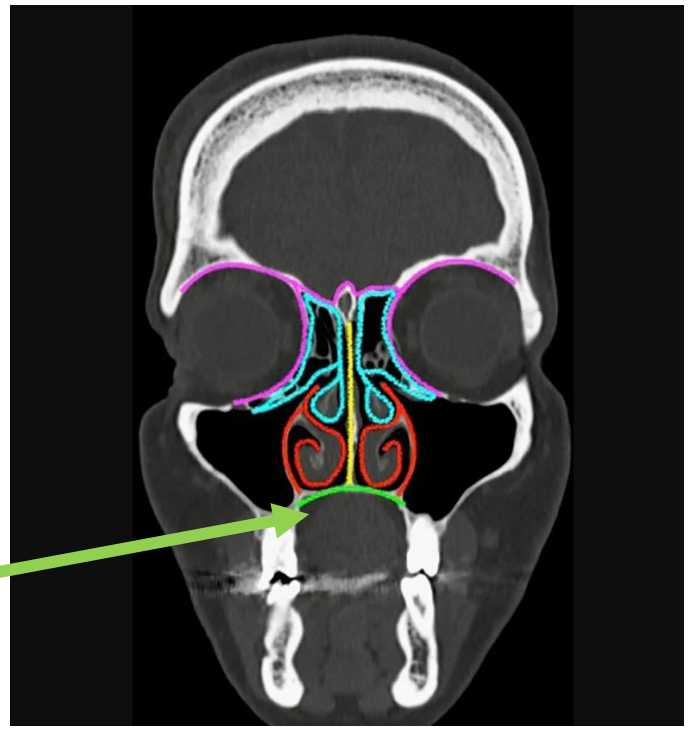
Letizia Nitro[1] · Carlotta Pipolo[1,2] · Gian Luca Fadda[2,3] · Fabiana Allevi[2,4] · Mario Borgione[3] · Giovanni Cavallo[3] · Giovanni Felisati[1,2] · Alberto Maria Saibene[1,2]



Signes fonctionnels aspécifiques : ulcérations, croutes nasales, sensation d'obstruction nasale, hyposmie, épistaxis, douleur nasale,...

Examen clinique avec performation plus ou moins étendue du septum

Avec des formes sévères : extension aux cornets moyens et supérieurs ou perforations palais



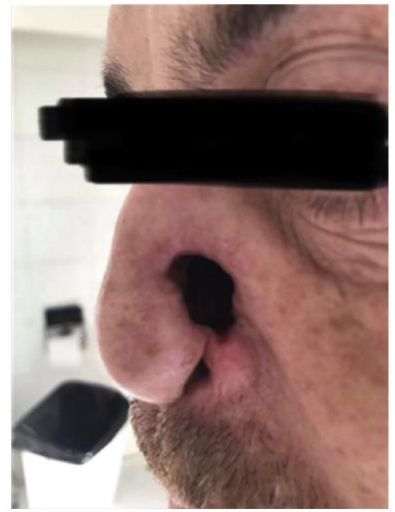


Fig. 1. Perforation de l'aile du nez.

Blaison et al, 2020

PHARMACOLOGIE CLINIQUE Marseille

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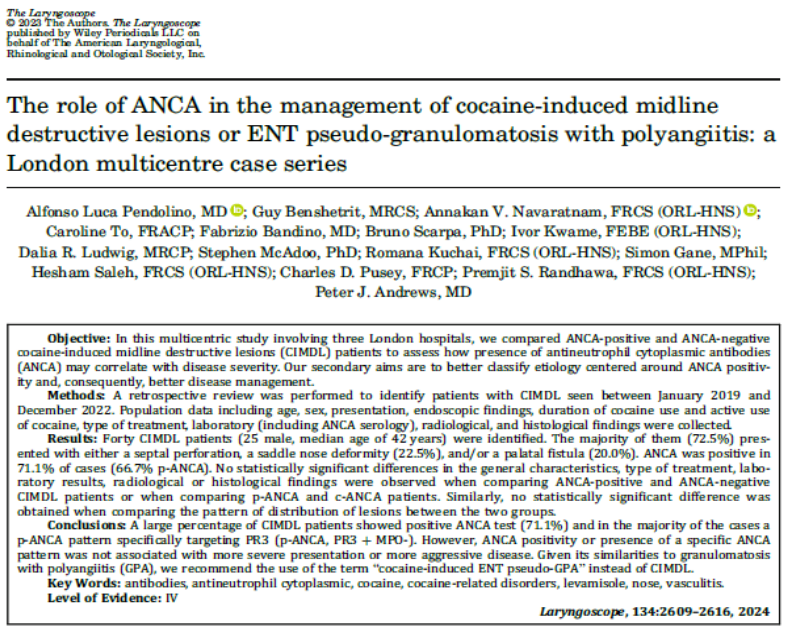
Institut de Neurosciences des Systèmes

2 formes :

Tableau clinique purement ORL (bilan biologique ANCA+, antiPR3+)

Tableau plus systémique avec atteinte cutanée, rénale, pulmonaire, neutropénie (ANCA+, antiPR3+ et antiMPO), consécutif à l'utilisation du lévamisole

Diagnostic différentiel : Vascularite à ANCA (maladie de Wégener)



The Laryngoscope

The role of ANCA in the management of cocaine-induced midline destructive lesions or ENT pseudo-granulomatosis with polyangiitis: a London multicentre case series

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Objective: In this multicentric study involving three London hospitals, we compared ANCA-positive and ANCA-negative cocaine-induced midline destructive lesions (CIMDL) patients to assess how presence of antineutrophil cytoplasmic antibodies (ANCA) may correlate with disease severity. Our secondary aims are to better classify etiology centered around ANCA positivity and, consequently, better disease management.

Methods: A retrospective review was performed to identify patients with CIMDL seen between January 2019 and December 2022. Population data including age, sex, presentation, endoscopic findings, duration of cocaine use and active use of cocaine, type of treatment, laboratory (including ANCA serology), radiological, and histological findings were collected.

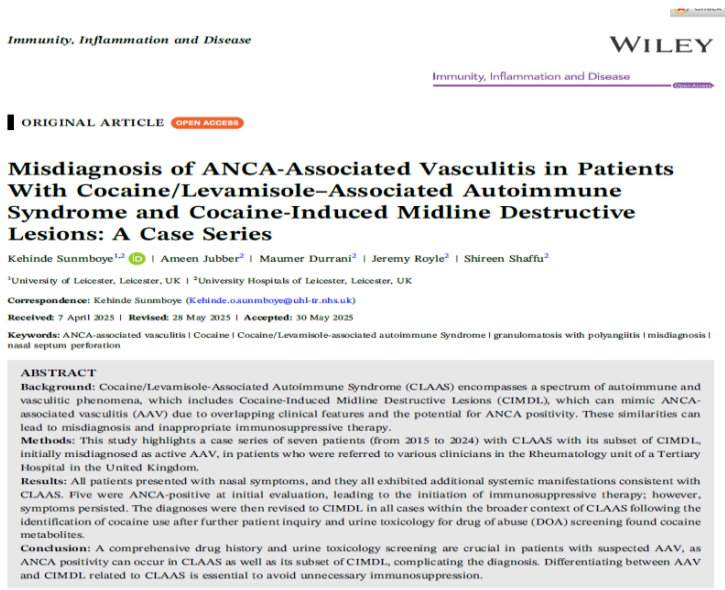
Results: Forty CIMDL patients (25 male, median age of 42 years) were identified. The majority of them (72.5%) presented with either a septal perforation, a saddle nose deformity (22.5%), and/or a palatal fistula (20.0%). ANCA was positive in 71.1% of cases (66.7% p-ANCA). No statistically significant differences in the general characteristics, type of treatment, laboratory results, radiological or histological findings were observed when comparing ANCA-positive and ANCA-negative CIMDL patients or when comparing p-ANCA and c-ANCA patients. Similarly, no statistically significant difference was obtained when comparing the pattern of distribution of lesions between the two groups.

Conclusions: A large percentage of CIMDL patients showed positive ANCA test (71.1%) and in the majority of the cases a p-ANCA pattern specifically targeting PR3 (p-ANCA, PR3 + MPO-). However, ANCA positivity or presence of a specific ANCA pattern was not associated with more severe presentation or more aggressive disease. Given its similarities to granulomatosis with polyangiitis (GPA), we recommend the use of the term "cocaine-induced ENT pseudo-GPA" instead of CIMDL.

Key Words: antibodies, antineutrophil cytoplasmic, cocaine, cocaine-related disorders, levamisole, nose, vasculitis.

Level of Evidence: IV

Laryngoscope, 134:2609–2616, 2024



Immunity, Inflammation and Disease

WILEY

Immunity, Inflammation and Disease

ORIGINAL ARTICLE OPEN ACCESS

Misdiagnosis of ANCA-Associated Vasculitis in Patients With Cocaine/Levamisole–Associated Autoimmune Syndrome and Cocaine-Induced Midline Destructive Lesions: A Case Series

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Keywords: ANCA-associated vasculitis | Cocaine | Cocaine/Levamisole-associated autoimmune Syndrome | granulomatosis with polyangiitis | misdiagnosis | nasal septum perforation

ABSTRACT

Background: Cocaine/Levamisole-Associated Autoimmune Syndrome (CLAAS) encompasses a spectrum of autoimmune and vasculitic phenomena, which includes Cocaine-Induced Midline Destructive Lesions (CIMDL), which can mimic ANCA-associated vasculitis (AAV) due to overlapping clinical features and the potential for ANCA positivity. These similarities can lead to misdiagnosis and inappropriate immunosuppressive therapy.

Methods: This study highlights a case series of seven patients (from 2015 to 2024) with CLAAS with its subset of CIMDL, initially misdiagnosed as active AAV, in patients who were referred to various clinicians in the Rheumatology unit of a Tertiary Hospital in the United Kingdom.

Results: All patients presented with nasal symptoms, and they all exhibited additional systemic manifestations consistent with CLAAS. Five were ANCA-positive at initial evaluation, leading to the initiation of immunosuppressive therapy; however, symptoms persisted. The diagnoses were then revised to CIMDL in all cases within the broader context of CLAAS following the identification of cocaine use after further patient inquiry and urine toxicology for drug of abuse (DOA) screening found cocaine metabolites.

Conclusion: A comprehensive drug history and urine toxicology screening are crucial in patients with suspected AAV, as ANCA positivity can occur in CLAAS as well as its subset of CIMDL, complicating the diagnosis. Differentiating between AAV and CIMDL related to CLAAS is essential to avoid unnecessary immunosuppression.

….ces complications ont été décrites en Asie avec l'usage de Kétamine dont l'usage régulier augmente en France

Various toxicities: case report

A 23-year-old man developed nasal septum perforation, urinary frequency, urinary urgency, supra-pubic pain and addiction following ketamine abuse with nasal insufflation.

The man presented to a clinic with a two month history of nasal obstruction and intermittent nasal bleeding. Additionally, he was suffering from urinary frequency, urinary urgency and supra-pubic pain. His medical history was non-significant for nasal trauma or any surgical procedure. Thereafter, he revealed that, he was addicted to ketamine powder for two years, and was consuming it via nasal snorting (right nostril) [*amount inhaled not stated*]. An endoscopic sinus examination demonstrated generalised mucosal necrosis, atrophy in his right nasal cavity along with septum perforation. The perforation was 2 × 1cm in size and enabled direct visualisation of the contralateral inferior turbinate. However, the mucosa in the left side was normal. Consequently, nasal septum perforation secondary to his right nostril dependent ketamine snorting was considered.

The man discontinued the use of ketamine leading to improvement in his nasal symptoms. During follow ups, he also received regular intranasal rinses and endoscopic debridement. However, only his urinary tract symptoms persisted.

Tsai K-K, et al. Ketamine-snorting-induced nasal septum perforation. Ear, Nose, and Throat Journal 95: 256, No. 7, Jan 2016 - Taiwan 803239078

J. Med. Toxicol. (2012) 8:267–270
DOI 10.1007/s13181-012-0229-z

TOXICOLOGY INVESTIGATION

Acute and Chronic Toxicity Pattern in Ketamine Abusers in Hong Kong

Yiu-Cheung Chan

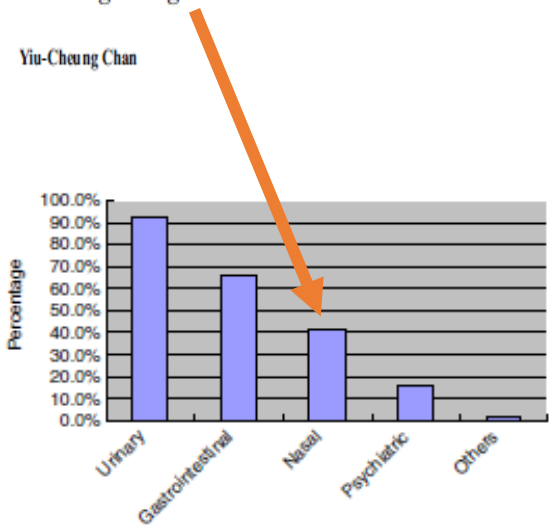


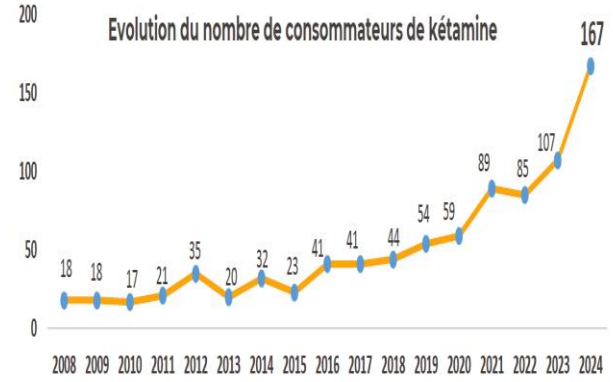
Fig. 4 Presenting symptoms of chronic cases

OPPIDUM

KÉTAMINE : UNE CONSOMMATION TOUJOURS EN AUGMENTATION

En 2024, 167 sujets sont consommateurs de kétamine (versus n=32 en 2014). 51% de ces sujets ont un usage quotidien ou hebdomadaire ; 33% déclarent une dépendance et 36% une souffrance à l'arrêt. Ces profils exposent davantage aux complications cliniques (uro-néphrologiques, hépatobiliaires). Six fois plus de sujets déclarent la kétamine comme 1er produit ayant entraîné une dépendance en deux ans (n=30 en 2024 versus n=5 en 2022).

On note également 3 consommations de dérivés de la kétamine : 2F-DCK (n=2), O-PCE(n=1).



	2022	2023	2024
Nombre de fiches	1498	1709	1756
COCAINE	696 (46.5%)	819 (47.9%)	884 (50.3%)
HEROINE	468 (31.2%)	509 (29.8%)	446 (25.4%)
KETAMINE	**74 (4.9%)**	**84 (4.9%)**	**141 (8.0%)**
SUBUTEX	72 (4.8%)	65 (3.8%)	89 (5.1%)
3-MMC	35 (2.3%)	32 (1.9%)	31 (1.8%)

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Les 5 points à retenir

- **Sévérité** : Les complications cliniques liées aux substances constituent une gravité/sévérité additionnelle

- **Diagnostic étiologique** : relier les complications à la consommation est essentiel sous peine de leur aggravation ou de leur récidive (*exemple de l'embolie pulmonaire sous protoxyde d'azote*) : d'où Informations/sensibilisation des usagers et des cliniciens

- **Bilan complet** : vision transversale/décloisonnée. Approche multidisciplinaire (Addictologue mais pas que…) liée aux atteintes combinées. *Exemple des usagers réguliers de kétamine avec atteintes urinaires, biliaires, nasales*

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- **Vigilance** : Contribuez à la sécurité sanitaire. N'hésitez pas à contacter/déclarer en addictovigilance www.addictovigilance.fr. Mieux connaitre ces complications et les faire connaitre

- **Soins** : A delà de leur prises en charge, ces complications peuvent aussi être un levier thérapeutique, une opportunité de rentrer dans le soin pour initier une prise en charge addictologique personnalisée

SANTE DES ADDICTIONS

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